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*Chest* 2008;134:255-262; Prepublished online April 10, 2008;  
DOI 10.1378/chest.07-2138

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## Comparison of a Combination of Tiotropium Plus Formoterol to Salmeterol Plus Fluticasone in Moderate COPD\*

Klaus F. Rabe, PhD, MD; Wolfgang Timmer, MD; Alexandros Sagkriotis, MSc; and Klaus Viel, MD

**Background:** A 6-week, multicenter, randomized, double-blind, parallel-group study was conducted in patients with COPD to compare lung function improvements of tiotropium, 18  $\mu\text{g}$  qd, plus formoterol, 12  $\mu\text{g}$  bid, to salmeterol, 50  $\mu\text{g}$  bid, plus fluticasone, 500  $\mu\text{g}$  bid.

**Methods:** Following a screening visit, subjects entered a run-in period in which they received regular ipratropium. At randomization, patients were assigned to either tiotropium plus formoterol or salmeterol plus fluticasone. After 6 weeks of treatment, a 12-h lung function profile was obtained. The coprimary end points were FEV<sub>1</sub> area under the curve for the time period 0 to 12 h (AUC<sub>0-12</sub>) and peak FEV<sub>1</sub>.

**Results:** A total of 729 patients were screened, and 605 patients were randomized and treated. A total of 592 patients (baseline FEV<sub>1</sub>, 1.32  $\pm$  0.43 L/min [ $\pm$ SD]) were included in the analysis. After 6 weeks, the 12-h lung function profiles in the group receiving tiotropium plus formoterol were superior to those in the group receiving salmeterol plus fluticasone (mean difference in FEV<sub>1</sub> AUC<sub>0-12</sub>, 78 mL [ $p$  = 0.0006]; mean difference in FVC AUC<sub>0-12</sub>, 173 mL,  $p$  < 0.0001). Also, peak responses were in favor of tiotropium plus formoterol (difference in peak FEV<sub>1</sub>, 103 mL [ $p$  < 0.0001]; difference in peak FVC, 214 mL [ $p$  < 0.0001]), as were FEV<sub>1</sub> and FVC at each individual time point after dose ( $p$  < 0.05). Predose FVC was significantly higher with the bronchodilator combination, while predose FEV<sub>1</sub> and rescue medication use did not differ significantly between groups. Both treatments were well tolerated.

**Conclusions:** Tiotropium plus formoterol was superior in lung function over the day compared to salmeterol plus fluticasone in patients with moderate COPD. Long-term studies in patients with severe COPD are warranted to assess the relative efficacy of different treatment combinations.

**Trial registration:** Clinicaltrials.gov Identifier: NCT00239421.

(CHEST 2008; 134:255-262)

**Key words:** combination treatment; COPD; fluticasone; formoterol; lung function; salmeterol; tiotropium

**Abbreviations:** AUC<sub>0-12</sub> = area under the curve for the time period 0 to 12 h; CI = confidence interval; FAS = full analysis set; PEF<sub>R</sub> = peak expiratory flow rate

International guidelines<sup>1,2</sup> for the treatment of COPD recommend pharmacologic therapy with one or more bronchodilators in patients with moderate disease, and addition of an inhaled corticosteroid in patients with severe or very severe COPD. Long-acting bronchodilators such as tiotropium, salmeterol, or formoterol are preferred over short-acting agents,<sup>1</sup> and have been demonstrated to ameliorate the symptoms of patients in numerous clinical trials.<sup>3-12</sup> Also, the addi-

tive effects of combinations of different classes of bronchodilators have been shown.<sup>13-15</sup> While long-acting bronchodilators have the potential to reduce exacerbations of COPD,<sup>16-19</sup> the increasing risk for exacerbations in more severe COPD provides the

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rationale for add-on treatment with an inhaled corticosteroid.<sup>18-21</sup> However, beyond the reduction of exacer-

bations, the combination of a long-acting  $\beta$ -agonist with an inhaled corticosteroid offered additional bronchodilator efficacy over the bronchodilator alone in several studies.<sup>18,21–23</sup>

We wondered whether maximal bronchodilatation can be achieved by a frequently prescribed combination of two long-acting bronchodilator drugs from different classes, or alternatively by a popular mixed combination including an inhaled corticosteroid. Hence, the present study compared the bronchodilator response of the combination of tiotropium, 18  $\mu\text{g}$  qd, plus formoterol, 12  $\mu\text{g}$  bid, to the combination of salmeterol, 50  $\mu\text{g}$  bid, plus fluticasone, 500  $\mu\text{g}$  bid. Serial spirometric measurements were conducted over 12 h after morning inhalation, when COPD patients are active and in most need of bronchodilation.

## MATERIALS AND METHODS

### *Study Objectives and Overall Design Description*

This was a 6-week, multicenter, randomized, double-blind, quadruple-dummy, parallel-group study in COPD patients conducted in eight countries between January 2004 and September 2004 (study code 205.287). The objective of the study was to compare the spirometric efficacy between treatment with tiotropium inhalation capsules, 18  $\mu\text{g}$  qd, plus formoterol inhalation capsules, 12  $\mu\text{g}$  bid, and salmeterol, 50  $\mu\text{g}$  bid via aerosol inhalation, plus fluticasone, 500  $\mu\text{g}$  bid, via aerosol inhalation.

Subjects entered a 2- to 4-week run-in period. At screening, pulmonary function tests were performed prior to and 60 min after inhalation of 80  $\mu\text{g}$  of ipratropium and 400  $\mu\text{g}$  of salbutamol. At the second clinical visit (baseline), predose lung function was assessed, and patients were randomized to blinded treat-

ment. After 3 weeks of treatment, predose FEV<sub>1</sub> and FVC were quantified and patient compliance was checked. After 6 weeks of treatment, serial pulmonary function tests were scheduled over 12 h after dosing.

The study was conducted according to the revised Declaration of Helsinki, the requirements of good clinical practice, and other international and local regulations. The study was sponsored by Boehringer Ingelheim and Pfizer.

### *Recruitment of Subjects*

Key inclusion criteria were age  $\geq$  40 years, a smoking history  $>$  10 pack-years, a diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease,<sup>1</sup> and a relatively stable airway obstruction with a postbronchodilator FEV<sub>1</sub>  $<$  80% of predicted normal<sup>24</sup> and FEV<sub>1</sub>/FVC  $<$  70% at visit 1, and predose FEV<sub>1</sub>  $\leq$  65% of predicted at visit 2.

Key exclusion criteria were a history of asthma or significant diseases other than COPD, and treatment with inhaled steroids within 2 months prior to screening or during the run-in period in order to avoid any bias potentially caused by residual effects, or by withdrawal of inhaled corticosteroids. Oral steroids were not allowed for a period of 6 weeks prior to the screening visit. Tiotropium was not allowed during the run-in period. Patients who had been receiving tiotropium before the study underwent a 4-week run-in period (patients not receiving tiotropium, 2 weeks) to ensure an adequate washout prior to the baseline lung function test.

### *Study Medication and Medication Restrictions*

During the run-in period, all patients received ipratropium, 40  $\mu\text{g}$  qd, on a regular basis. On days 1 to 41, the study medication was administered according to a quadruple-dummy design as follows: the patients inhaled one capsule (tiotropium or matching placebo) using the HandiHaler device (Boehringer-Ingelheim; Ingelheim, Germany) once daily in the morning, one capsule (formoterol or matching placebo) using the Foradil Aerolizer (Novartis Pharmaceuticals; East Hanover, NJ) device twice daily, and two inhalations from each metered-dose inhaler (salmeterol or matching placebo, fluticasone or matching placebo) twice daily in the morning and in the evening, with a dosing interval of about 12 h. On day 42 (visit 4), a predose pulmonary function testing was performed prior to the last morning inhalation and the subsequent 12-h spirometry.

At all clinical visits, the investigator monitored the inhalation procedure and reinforced correct inhalation technique. During the entire study period, patients recorded daily rescue salbutamol use and peak flow rates on their diary cards. The following medications were prohibited during the study: inhaled steroids other than the study medication, oral steroids (except for the control of acute exacerbations as deemed medically necessary),  $\beta$ -agonists and anticholinergics other than the supplied rescue medication and study medication, and once-a-day theophylline preparations.

### *Spirometry*

Pulmonary function was assessed at each of the four visits using calibrated spirometers with the patient in a seated position having abstained from salbutamol for at least 8 h. The highest FEV<sub>1</sub> and the highest FVC each obtained on any of three tests meeting American Thoracic Society criteria<sup>25</sup> were recorded and normalized according to established standards.<sup>24</sup>

Time points were "predose" in the morning, and 60 min after bronchodilation with 400  $\mu\text{g}$  of salbutamol and 80  $\mu\text{g}$  of ipratro-

\*From the Department of Pulmonology (Dr. Rabe), Leiden University Medical Center, Leiden, the Netherlands; and Boehringer Ingelheim Pharma (Drs. Timmer and Viel, and Mr. Sagkriotis), Ingelheim, Germany.

This study was supported by Boehringer Ingelheim (Ingelheim, Germany) and Pfizer, New York, NY.

Professor Rabe has consulted, participated in Advisory Board Meetings and, received lecture fees from AstraZeneca, Boehringer, Chiesi Pharmaceuticals, Pfizer, Novartis, AltanaPharma, MSD, and GSK. Professor Rabe holds no stock or other equities in pharmaceutical companies. The Department of Pulmonology, and thereby professor Rabe as head of the department, has received grants from Novartis, AstraZeneca, Boehringer Ingelheim, Roche, and GSK in the years 2005 until 2008. Dr. Viel is an employee of Boehringer-Ingelheim Pharma, the manufacturer of tiotropium. Dr. Timmer was an employee of Boehringer-Ingelheim when this article was written. Mr. Sagkriotis has been employed by Boehringer-Ingelheim since January 1, 2005. Manuscript received October 2, 2007; revision accepted March 3, 2008.

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Correspondence to: Klaus F. Rabe, PhD, MD, Department of Pulmonology C3-P, Leiden University Medical Center, Albinusdreef 2 Postbus, NL-2300 Leiden, the Netherlands; e-mail: [k.f.rabe@lumc.nl](mailto:k.f.rabe@lumc.nl)

DOI: 10.1378/chest.07-2138

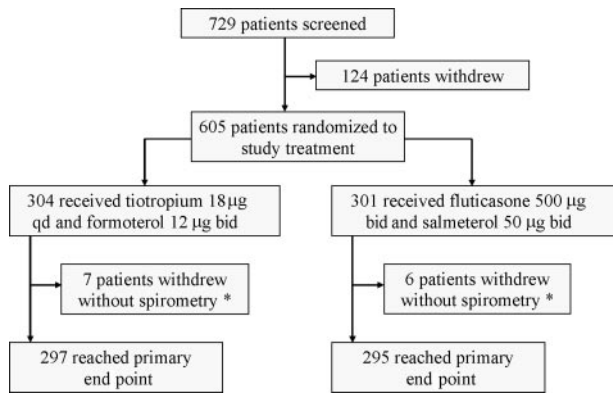


FIGURE 1. Patient flow. \*Total premature withdrawals: tiotropium plus formoterol, n = 16; fluticasone and salmeterol, n = 15.

pium at visit 1 (screening), predose in the morning at visit 2 (baseline) and at visit 3 (interim), and predose and repetitively for 12 h after inhalation of the study medication at visit 4 (end point). There were two prespecified primary end points: FEV<sub>1</sub> area under the curve for the time period 0 to 12 h (AUC<sub>0–12</sub>) and peak FEV<sub>1</sub>, both assessed after 6 weeks of treatment. Key secondary efficacy end points were peak FVC and FVC AUC<sub>0–12</sub> after 6 weeks of treatment, and morning predose FEV<sub>1</sub> and FVC at 3 weeks and 6 weeks.

#### Diary Cards

Patients recorded on daily diary cards their morning and evening peak expiratory flow rates (PEFRs), the number of salbutamol metered-dose inhaler puffs inhaled, and the study medication received.

#### Safety Measurements

Pulse rate and BP was measured at each visit. A physical examination was completed on all patients at screening and repeated at the end of patient participation. Adverse events were monitored and recorded using standardized procedures.

#### Statistical Analysis

The required sample size per arm was estimated to be 219 evaluable treated patients to detect a difference between tiotropium plus formoterol and salmeterol plus fluticasone in both primary end points of 70 mL (assumed SD, 225 mL; power = 0.90). The level of significance was set to  $\alpha = 0.05$  (two sided). The FEV<sub>1</sub> AUC<sub>0–12</sub> was calculated as area under the curve from predose to 12 h using the trapezoidal rule divided by full duration. Peak FEV<sub>1</sub> was defined as the maximum postdose FEV<sub>1</sub> obtained within the first 3 h of testing.

Missing spirometry data for which there were data from the visit both before and after were linearly interpolated. If all subsequent readings for that visit were missing, then the last observation-carried-forward procedure was used. Data missing due to lack of efficacy, safety concerns, or after inhalation of rescue medication were replaced with the least favorable data for that visit.

In the analysis of efficacy, all patients with baseline data and any data following multiple doses were included (full analysis set[FAS]). Efficacy end points were evaluated by an analysis of covariance model. The statistical model included the factors treatment, center, and baseline reading as covariables. The least-square means adjusted for center and baseline values were obtained. The mean square error was used as the error term, and two-sided 95% confidence intervals (CIs) were calculated for the treatment contrast of interest. *Post hoc* subgroup analyses by severity and acute bronchodilator response were performed with respect to FEV<sub>1</sub> and FVC findings. The safety end points were evaluated descriptively. Statistical analysis was performed (SAS version 8.01; SAS Institute; Cary, NC).

## RESULTS

### Data Sets Analyzed, Demographics, and Baseline Disease Characteristics

Seven hundred twenty-nine patients were screened, and 605 patients were randomized and treated; 95% of patients completed the study (Fig 1). The two treatment groups were comparable with regard to demographic data, smoking history, duration of COPD, and acute response to bronchodilators (Table 1). Patients were considered “reversible” if they demonstrated a

Table 1—Baseline Demographics, Disease Characteristics, and Screening Pulmonary Function Data (Safety Set)

Variables	Tiotropium Plus Formoterol	Salmeterol Plus Fluticasone	Total
Total treated, No.	304	301	605
Gender, No. (%)			
Male	213 (70)	201 (67)	414 (68)
Female	91 (30)	100 (33)	191 (32)
Mean age $\pm$ SD, yr	62 $\pm$ 9	62 $\pm$ 9	62 $\pm$ 9
Median smoking history (range), pack-yr	40 (11–196)	40 (11–135)	40 (11–196)
Median duration of COPD (range), mo	75 (1–444)	74 (1–504)	74 (1–504)
Mean FEV <sub>1</sub> before bronchodilator $\pm$ SD, L	1.38 $\pm$ 0.47	1.38 $\pm$ 0.43	1.38 $\pm$ 0.45
Mean FEV <sub>1</sub> after bronchodilator $\pm$ SD, L	1.61 $\pm$ 0.51	1.61 $\pm$ 0.48	1.61 $\pm$ 0.50
Mean FEV <sub>1</sub> % predicted after bronchodilator $\pm$ SD, %	55 $\pm$ 14	56 $\pm$ 13	55 $\pm$ 13
Mean FEV <sub>1</sub> /FVC % predicted after bronchodilator $\pm$ SD, %	52 $\pm$ 10	52 $\pm$ 10	52 $\pm$ 10
Reversible* patients, No. (%)	148 (49)	150 (50)	298 (49)

\*FEV<sub>1</sub> change from baseline  $\geq$  12% and FEV<sub>1</sub> increase  $\geq$  200 mL following salbutamol and ipratropium at screening.

**Table 2—Key Efficacy Results on Day 42 (FAS Population)\***

Variables	Tiotropium-Plus-Formoterol Group	Common Baseline, Visit 2	Salmeterol-Plus-Fluticasone Group	Statistical Significance
Lung function				
FEV <sub>1</sub> , L		1.32		
FVC, L		2.69		
Copriary end points				
FEV <sub>1</sub> AUC <sub>0-12h</sub> , L	1.64 ± 0.02		1.56 ± 0.02	p = 0.0006
Peak FEV <sub>1</sub> , L	1.78 ± 0.02		1.67 ± 0.02	p < 0.0001
Secondary end points				
FVC AUC <sub>0-12h</sub> , L	3.14 ± 0.03		2.97 ± 0.03	p < 0.0001
Peak FVC, L	3.38 ± 0.03		3.16 ± 0.03	p < 0.0001
Predose FEV <sub>1</sub> , L	1.51 ± 0.02		1.49 ± 0.02	Not significant
Predose FVC, L	2.95 ± 0.03		2.87 ± 0.03	p = 0.0228

\*All end point data are expressed as adjusted means ± SE on day 42.

relative FEV<sub>1</sub> increase by ≥ 12% and an absolute FEV<sub>1</sub> increase by ≥ 200 mL.

Lung function data at screening (visit 1) for randomized patients are summarized in Table 1. At visit 2 (baseline), following a run-in period of at 2 weeks or 4 weeks, the predose FEV<sub>1</sub> was 1.32 ± 0.43 L. Overall, the two treatment groups were comparable with respect to baseline pulmonary function characteristics.

### Spirometry Outcomes

All results are expressed as adjusted means (baseline, center). For an overview, refer to Table 2. The 12-h FEV<sub>1</sub> profile after 6 weeks was generally higher in the tiotropium-plus-formoterol treatment group than in the salmeterol-plus-fluticasone group (Fig 2). The FEV<sub>1</sub> AUC<sub>0-12h</sub> mean difference was 78 mL higher (95% CI, 34 to 122 mL) under treatment with tiotropium plus formoterol as compared to salmeterol plus fluticasone (p = 0.0006). The difference in peak FEV<sub>1</sub> was 103 mL (95% CI, 55 to 150 mL) in favor of tiotropium plus formoterol (p < 0.0001).

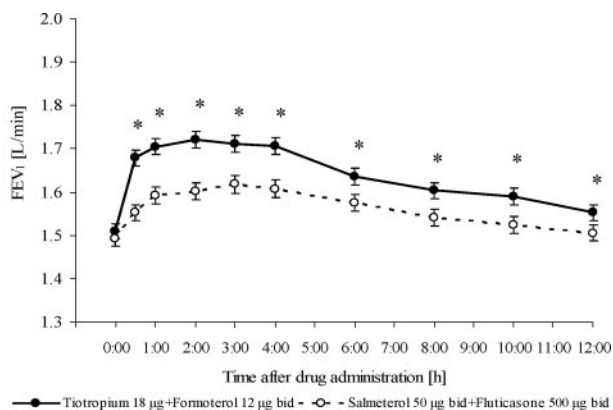


FIGURE 2. Adjusted means (± SE) of FEV<sub>1</sub> in liters per minute over time on day 42 (FAS population). \*p < 0.05 between treatment groups (bars represent SE).

The 12-h FVC profiles after 6 weeks are displayed in Figure 3. Tiotropium plus formoterol was markedly superior with regard to the 12-h FVC profile (difference, 173 mL [95% CI, 104 to 242 mL, p < 0.0001]; p < 0.05 for each individual time point) and peak FVC (difference, 214 mL [95% CI, 137 to 291 mL, p < 0.0001]). Also, morning predose FEV<sub>1</sub> tended to be higher in patients receiving tiotropium plus formoterol (mean, 16 mL [95% CI, -25 to 58 mL, p > 0.05]). The difference in predose FVC after 6 weeks favored tiotropium plus formoterol (mean, 79 mL [95% CI, 11 to 147 mL, p < 0.05]). Predose spirometry after 3 weeks showed similar results.

In a *post hoc* analysis, the lung function profile observed with the two treatments over the day was compared in subgroups according to acute bronchodilator response, and by severity. The spirometric response to tiotropium plus formoterol was generally higher (Table 3).

### Explorative End Points

For both treatments, morning and evening PEFr increased over time. The differences in evening

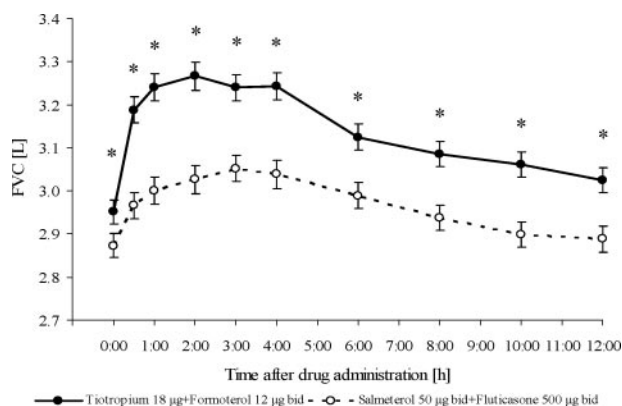


FIGURE 3. Adjusted means (± SE) of FVC in liters over time on day 42 (FAS population); \*p < 0.05 between treatment groups (bars represent SE).

Table 3—Key Efficacy Results: Subgroups by Acute Bronchodilator Response and Severity\*

Variables	Short-Term Response§ (n = 292)			Poor Short-Term Response§ (n = 300)			Moderate COPD† (n = 399)			Severe or Very Severe COPD† (n = 193)		
	Tiotropium-Plus-Formoterol Group	Salmeterol-Plus-Fluticasone Group	Common Baseline	Tiotropium-Plus-Formoterol Group	Salmeterol-Plus-Fluticasone Group	Common Baseline	Tiotropium-Plus-Formoterol Group	Salmeterol-Plus-Fluticasone Group	Common Baseline	Tiotropium-Plus-Formoterol Group	Salmeterol-Plus-Fluticasone Group	Common Baseline
Lung function												
FEV <sub>1</sub> , L	1.74 ± 0.03†	1.66 ± 0.03	1.34	1.54 ± 0.02†	1.46 ± 0.02	1.29	1.84 ± 0.02†	1.77 ± 0.02	1.48	1.22 ± 0.03†	1.15 ± 0.03	0.99
FVC, L	1.90 ± 0.03†	1.77 ± 0.03	2.80	1.65 ± 0.02†	1.57 ± 0.02	2.58	1.98 ± 0.02†	1.89 ± 0.03	2.86	1.35 ± 0.03†	1.24 ± 0.03	2.32
Day 42												
FEV <sub>1</sub> AUC <sub>0-12</sub> , L	3.39 ± 0.04†	3.19 ± 0.04		2.89 ± 0.04†	2.75 ± 0.04		3.33 ± 0.03†	3.18 ± 0.04		2.76 ± 0.05†	2.56 ± 0.05	
Peak FEV <sub>1</sub> , L	3.63 ± 0.05†	3.39 ± 0.05		3.12 ± 0.04†	2.93 ± 0.04		3.55 ± 0.04†	3.38 ± 0.04		3.01 ± 0.06†	2.74 ± 0.06	
FVC AUC <sub>0-12</sub> , L	1.58 ± 0.03	1.56 ± 0.03		1.44 ± 0.02	1.42 ± 0.02		1.70 ± 0.02	1.68 ± 0.02		1.12 ± 0.03	1.11 ± 0.03	
Peak FVC, L	3.15 ± 0.04	3.06 ± 0.04		2.76 ± 0.04	2.68 ± 0.04		3.15 ± 0.03	3.09 ± 0.03		2.53 ± 0.05	2.44 ± 0.05	
Predose FEV <sub>1</sub> , L												
Predose FVC, L												

\*All end point data for tiotropium plus formoterol and salmeterol plus fluticasone are expressed as adjusted means ± SE.

†p < 0.05 (tiotropium plus formoterol vs salmeterol plus fluticasone).

‡Threshold FEV<sub>1</sub> of < 50% of predicted at visit 1.

§Threshold of short-term response ≥ 12% of baseline FEV<sub>1</sub> and ≥ 200 mL after salbutamol and ipratropium.

PEFR between the two treatment arms ranged from 6.6 L/min (95% CI, 0.2 to 13.0 L/min) at week 5, to 8.1 L/min (95% CI, 2.3 to 13.9 L/min) at week 3 in favor of tiotropium plus formoterol ( $p < 0.05$ ). There were no significant differences between the two treatment groups in morning PEFr.

The use of rescue medication was similarly low in both treatment arms, with no significant differences over the day or during the night. For both treatment arms, the compliance as recorded in the diaries was 99%. The number of tiotropium and formoterol powder capsules returned mirrored the patients' records.

### Safety and Tolerability

Eighty-seven patients (28.5%) in the tiotropium-plus-formoterol group, and 84 patients (27.8%) in the fluticasone-plus-salmeterol group reported an adverse event. Individual adverse events with a frequency  $\geq 3\%$  in the treatment groups were COPD exacerbation (4.3% and 5.0%, respectively) and pharyngitis (3.9% and 4.6%, respectively). Dry mouth was reported in four patients in both treatment arms. Six patients in either treatment group had serious adverse events. One patient in each group died (myocardial infarction, bronchial cancer).

## DISCUSSION

In this study over 6 weeks in patients with moderate-to-severe COPD, the combination of tiotropium once daily plus formoterol twice daily showed a significantly greater effect on postdose lung function, compared to salmeterol bid plus fluticasone twice daily. Differences in favor of tiotropium plus formoterol were maintained over 12 h following the morning dose. Spirometric benefits were substantiated by superior FVC improvements that allowed even better differentiation from salmeterol plus fluticasone.

In previous placebo-controlled studies<sup>18,21–23</sup> in moderate-to-severe COPD, the fixed combination of salmeterol plus fluticasone consistently improved the FEV<sub>1</sub> of COPD patients more than the individual components alone. The postdose treatment effect of salmeterol plus fluticasone after 6 months was 231 mL in a study conducted by Mahler et al,<sup>22</sup> and approximately 150 mL in 1-year studies<sup>21,26</sup> with formoterol plus budesonide. The effects on FVC were not reported from these studies. Monotherapy with the long-acting anticholinergic tiotropium improved postdose FEV<sub>1</sub> after 1 year by 210 mL,<sup>3</sup> with a substantial parallel increase in the FVC up to 440 mL. More recently, superior bronchodilator effects of a free combination of tiotropium plus formoterol

over the individual components were reported from a short-term study,<sup>14</sup> which revealed a treatment response of 354 mL for FEV<sub>1</sub> and 678 mL for FVC above baseline. In the current study focusing on patients with moderate COPD, the absolute improvements in postdose FEV<sub>1</sub> (457 mL) and FVC (691 mL) observed in the tiotropium-plus-formoterol group were among the highest reported from COPD studies so far.

These findings underline the partly reversible character of the airflow limitation in COPD. Forty-nine percent of patients randomized to our trial demonstrated at least a 12% (and 200 mL) increase in FEV<sub>1</sub> following two classes of short-acting bronchodilators (salbutamol and ipratropium). "Significant reversibility" has previously been reported for approximately one third of COPD patients,<sup>27</sup> and is no longer considered a standard diagnostic criterion in COPD.<sup>1</sup>

The two regimens compared in this study mirror two popular inhaled-combination treatments in COPD in 2003. While tiotropium-plus-formoterol treatment follows the Global Initiative for Chronic Obstructive Lung Disease guideline<sup>1</sup> to consider a second bronchodilator in moderate COPD in order to optimize the symptom benefit for patients, the salmeterol-plus-fluticasone combination reflects the inhaled corticosteroid recommendation in severe and very severe COPD, when patients exacerbate more frequently. Nevertheless, inhaled corticosteroids and "fixed combinations" comprising an inhaled corticosteroid are frequently prescribed in earlier stages of COPD. Hence, this study was designed to directly compare the "different treatment paradigms" in patients with moderate COPD, when lung function improvement over the day, and symptom control are the predominant treatment goals. The improvements in the 12-h lung function relative to salmeterol plus fluticasone, observed in patients treated with tiotropium plus formoterol, were robust over the day, across severity stages of COPD, and independent of acute bronchodilator response. In particular, the superior improvements in FVC with tiotropium plus formoterol are considered meaningful because FVC is an indirect measure of air trapping due to premature airway closure.<sup>28,29</sup> Less air trapping, *ie*, reduced hyperinflation, translates into less dyspnea and increased exercise endurance with favorable implications on the deconditioning of COPD patients.<sup>6,30,31</sup>

With regard to the amount of salbutamol inhalation on demand, there were no significant differences between the two treatment groups. However, all patients received effective bronchodilator treatment that diminished rescue medication usage in the majority of patients, *ie*, differences between treatments were compared on a high level of control. This

was reflected by a median of 100% salbutamol-free nights per patient in both treatment arms after randomization, and a median of 85% (tiotropium plus formoterol) and 81% (salmeterol plus fluticasone) salbutamol-free days, respectively. Additionally, PEFs between treatment groups were similar in the morning but increased more over the day in patients treated with the bronchodilator combination.

Our study has several limitations: (1) due to the complex schedule of truly blinded inhaled treatments, comparison of combination therapy in COPD is a challenge for patients, investigators, and the logistic support; this trial used a quadruple-dummy design that did not pose a compliance issue during 6 weeks of treatment but would have limited the feasibility of a longer-term study; (2) for the above reason, lung function effects were compared after 6 weeks of treatment, even though the chronic progressive character of the disease would have favored a longer observation period; while long-term treatment effects may not have unfolded after 6 weeks, previous spirometry studies indicate that the major improvement in FEV<sub>1</sub> materializes within 6 weeks of start of fluticasone and salmeterol treatment,<sup>22</sup> and tiotropium treatment<sup>3</sup>; (3) there was no placebo control group in the study. However, placebo controls are increasingly difficult to justify in COPD studies, particularly if treatments tested do not allow state-of-the-art concomitant medication; (4) the evaluation of the contribution of single-treatment components forming the combination therapies is limited in the study because different long-acting  $\beta$ -agonists and different devices were used in the two treatment arms. Since the aim of our study was to compare popular combination therapies, and blinded Diskus devices were not available at the time of conduct, a strict analytical trial design could not be followed. Future studies to assess the relative efficacy of the different treatment paradigms would optimally limit the number of variables by applying the same long-acting  $\beta$ -agonist in both treatment groups, and comparable device technology. Strengths of our study are as follows: (1) the rigorous 12-h spirometry that captured the most relevant over-the-day lung function profile, and (2) the full FVC data set obtained that indirectly monitored air trapping in the large-scale multicenter setting.

In conclusion, the combination of once-daily tiotropium plus twice-daily formoterol was superior to a twice-daily combination of salmeterol and fluticasone in daytime lung function outcomes over 6 weeks. Differences are considered meaningful and support current treatment recommendations in moderate COPD to combine two bronchodilators of different classes rather than to add an inhaled corti-

costeroid, if maintenance treatment with a single long-acting bronchodilator does not suffice. Further longer-term studies to assess the relative efficacy of a dual bronchodilator combination vs a mixed combination on quality of life and exacerbations in patients with severe and very severe COPD are needed to assess if optimal bronchodilation translates into a reduced risk for exacerbations, and a better health-related quality of life.

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**Comparison of a Combination of Tiotropium Plus Formoterol to Salmeterol Plus Fluticasone in Moderate COPD**

Klaus F. Rabe, Wolfgang Timmer, Alexandros Sagkriotis and Klaus Viel  
*Chest* 2008;134;255-262; Prepublished online April 10, 2008;  
DOI 10.1378/chest.07-2138

**This information is current as of September 28, 2008**

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