The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 24, 2011 VOL. 364 NO. 12

Tiotropium versus Salmeterol for the Prevention of Exacerbations of COPD

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ABSTRACT

BACKGROUND

Treatment guidelines recommend the use of inhaled long-acting bronchodilators to alleviate symptoms and reduce the risk of exacerbations in patients with moderate-to-very-severe chronic obstructive pulmonary disease (COPD) but do not specify whether a long-acting anticholinergic drug or a β_2-agonist is the preferred agent. We investigated whether the anticholinergic drug tiotropium is superior to the β_2-agonist salmeterol in preventing exacerbations of COPD.

METHODS

In a 1-year, randomized, double-blind, double-dummy, parallel-group trial, we compared the effect of treatment with 18 μg of tiotropium once daily with that of 50 μg of salmeterol twice daily on the incidence of moderate or severe exacerbations in patients with moderate-to-very-severe COPD and a history of exacerbations in the preceding year.

RESULTS

A total of 7376 patients were randomly assigned to and treated with tiotropium (3707 patients) or salmeterol (3669 patients). Tiotropium, as compared with salmeterol, increased the time to the first exacerbation (187 days vs. 145 days), with a 17% reduction in risk (hazard ratio, 0.83; 95% confidence interval [CI], 0.77 to 0.90; P<0.001). Tiotropium also increased the time to the first severe exacerbation (hazard ratio, 0.72; 95% CI, 0.61 to 0.85; P<0.001), reduced the annual number of moderate or severe exacerbations (0.64 vs. 0.72; rate ratio, 0.89; 95% CI, 0.83 to 0.96; P=0.002), and reduced the annual number of severe exacerbations (0.09 vs. 0.13; rate ratio, 0.73; 95% CI, 0.66 to 0.82; P<0.001). Overall, the incidence of serious adverse events and of adverse events leading to the discontinuation of treatment was similar in the two study groups. There were 64 deaths (1.7%) in the tiotropium group and 78 (2.1%) in the salmeterol group.

CONCLUSIONS

These results show that, in patients with moderate-to-very-severe COPD, tiotropium is more effective than salmeterol in preventing exacerbations. (Funded by Boehringer Ingelheim and Pfizer; ClinicalTrials.gov number, NCT00563381.)

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N Engl J Med 2011;364:1093-103.

Chronic obstructive pulmonary disease (COPD) is a leading cause of disability and death worldwide.[1-3] Exacerbations of COPD indicate instability or worsening of the patient's clinical status and progression of the disease and have been associated with the development of complications, an increased risk of subsequent exacerbations, a worsening of coexisting conditions, reduced health status and physical activity, deterioration of lung function, and an increased risk of death.[4-7] The prevention of exacerbations therefore constitutes a major goal of treatment.[1,2]

Therapy with a long-acting anticholinergic drug or a long-acting β_2-agonist is recommended as first-line maintenance therapy in patients with moderate-to-very-severe COPD,[1,2] since both of these drugs reduce symptoms, improve quality of life and lung function, and reduce the risk of exacerbations and hospitalizations.[8-12] However, treatment guidelines do not specify whether a long-acting anticholinergic drug or a β_2-agonist is the preferred agent.[1,2]

Comparative studies have indicated that tiotropium is associated with a greater reduction in the risk of exacerbations and exacerbation-related hospitalizations than is salmeterol, although the differences were not significant.[13,14] These were short-term studies (3 to 6 months in duration) and were not designed and powered to detect a difference in the risk of exacerbations. The Prevention of Exacerbations with Tiotropium in COPD (POET-COPD) trial was specifically designed to directly compare the effects of tiotropium with those of salmeterol on the risk of moderate and severe exacerbations. A placebo group was not included in the study, since there is substantial evidence of the superiority of both tiotropium and salmeterol over placebo.[8,12] Furthermore, a comparison of two active-treatment groups is in line with the recently growing relevance of comparative-effectiveness research to guidance regarding treatment decisions.[15,16]

Methods

Study Design and Oversight

We conducted a 1-year, randomized, double-blind, double-dummy, parallel-group trial at 725 centers in 25 countries to compare the effect of tiotropium (Spiriva, Boehringer Ingelheim) with that of salmeterol (Serevent, GlaxoSmithKline) on moderate and severe exacerbations of COPD (hereinafter called exacerbations) in patients with moderate-to-very-severe COPD.[17] The study was conducted in accordance with the provisions of the Declaration of Helsinki (1996) and Good Clinical Practice guidelines. All patients provided written informed consent before any study procedure was performed. The scientific steering committee (which was made up of two of the academic investigators and an external clinical researcher) and three employees of Boehringer Ingelheim developed the design and concept of the study, approved the statistical plan, had full access to the data, and interpreted the data. Onsite monitoring and site management were supported by a contract research organization (PAREXEL). The first draft of the manuscript and subsequent revisions were written by all the authors, and all the authors made the decision to submit the manuscript for publication. The statistical analysis was performed by an employee of the sponsor. All the authors had full access to the data and vouch for the accuracy and completeness of the data and the analyses, as well as the fidelity of the study to the protocol. (The protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org.) An independent ethics committee or institutional review board at each participating center reviewed and approved the protocol before commencement of the study. In addition, an independent data and safety monitoring board and a mortality adjudication committee were established (Section 10 in the Supplementary Appendix, available at NEJM.org).

End Points

The primary end point was the time to the first exacerbation of COPD. The time to the first exacerbation was selected as the primary end point because it is less likely to be affected by the introduction of additional therapies or by the occurrence of multiple exacerbations in some patients.[17] Secondary and safety end points included time-to-event end points, number-of-event end points, serious adverse events, and death (Section 2 in the Supplementary Appendix).

An exacerbation was defined as an increase in or new onset of more than one symptom of COPD (cough, sputum, wheezing, dyspnea, or chest tightness), with at least one symptom lasting 3 days or more and leading the patient's attending physician to initiate treatment with

systemic glucocorticoids, antibiotics, or both (criterion for moderate exacerbation) or to hospitalize the patient (criterion for severe exacerbation). The determination of the end of the exacerbation was made on the basis of the clinical assessment of the investigator. Data on exacerbations (according to the trial definition), as well as health care resources used to treat these exacerbations, were collected by means of a questionnaire that was administered during regular clinic visits and telephone contacts. When an investigator reported a case of pneumonia, he or she was questioned as to whether the event had been confirmed by imaging.

PATIENTS

Patients were eligible for inclusion in the study if they were at least 40 years of age and had a smoking history of 10 pack-years or more, a diagnosis of COPD, a forced expiratory volume in 1 second (FEV_1) after bronchodilation of ¨70% of the predicted value,[18] a ratio of FEV_1 to forced vital capacity (FVC) of ¨70%, and a documented history of at least one exacerbation leading to treatment with systemic glucocorticoids or antibiotics or hospitalization within the previous year. Spirometry (FEV_1 and FVC) was performed at the screening visit according to the guidelines of the American Thoracic Society[1] and was used only for the assessment of the severity of COPD. Postbronchodilator measurements were performed 30 minutes after the patient inhaled 400 μg of albuterol. Daily peak flow was recorded over the course of 4 months in a subgroup of patients, in conjunction with a genotyping analysis (for details, see Section 5 in the Supplementary Appendix); those data are not reported here. Full details regarding the exclusion criteria are provided in Section 6 in the Supplementary Appendix.

PROCEDURES

After a 2-week run-in period, eligible patients were randomly assigned to receive, for 1 year, either 18 μg of tiotropium once daily, delivered through the HandiHaler inhalation device (Boehringer Ingelheim), plus placebo twice daily, delivered through a pressurized, metered-dose inhaler, or 50 μg of salmeterol twice daily, delivered through a pressurized, metered-dose inhaler, plus placebo once daily, delivered through the HandiHaler device (for details, see Section 7 in the Supplementary Appendix). All the patients were given instruction in the use of the HandiHaler and pressurized, metered-dose inhaler devices at visits 1 (screening) and 2 (randomization). Concomitant medication at baseline was defined as the therapy the patients were receiving at the time of the screening visit (visit 1). During the run-in period, patients who were receiving tiotropium were required to switch to 40 μg of ipratropium four times a day, and this therapy was discontinued at the time of randomization. Patients who were receiving a long-acting β_2-agonist were permitted to continue the use of that medication during the run-in period. Patients receiving fixed-dose combinations of long-acting β_2-agonists and inhaled glucocorticoids were instructed to switch to inhaled glucocorticoid monotherapy at the start of the treatment phase of the study. Patients were allowed to continue their usual medications for COPD, except for anticholinergic drugs and long-acting β_2-agonists, during the double-blind treatment phase.

After randomization, clinic visits were scheduled at months 2, 4, 8, and 12, and monthly telephone calls were scheduled between visits. Patients completed a daily diary, and records were reviewed at each study visit to assess adherence to treatment and to determine whether respiratory symptoms met the criteria for exacerbation. Adherence was not systematically assessed during the trial. During clinic visits and monthly telephone calls, a questionnaire was administered to collect details regarding exacerbations of COPD. Adverse events leading to the discontinuation of treatment and serious adverse events including fatal events were recorded at the time of each clinic visit. Patients who prematurely discontinued treatment were followed for vital status (i.e., whether they were alive and, if they had died, the primary cause of death) until the end of the planned treatment period of 360 days. Information on vital status was considered to be complete for patients who attended all trial visits through day 360 and for those who prematurely discontinued study medication but whose vital status was confirmed at day 360. Details of the randomization procedures and of the procedures for concealing the treatment assignments are provided in Section 8 in the Supplementary Appendix.

STATISTICA• ANA•YSIS

We estimated that with a sample size of approximately 6800 patients (3400 in each treatment

group), the study would have 80% power to detect a 10% reduction with tiotropium as compared with salmeterol in the risk of a first exacerbation, with a two-sided test for the null hypothesis of a hazard ratio of 1 at a significance level of 0.05. A prespecified reestimation of the sample size (with the treatment assignments concealed) on the basis of the predicted event rate was performed toward the end of the originally planned recruitment phase and resulted in an increase of the sample size to a total of 7350 patients (Section 9 in the Supplementary Appendix).

The efficacy and safety analyses included all the patients who underwent randomization and who received at least one dose of the study medication. Primary and secondary time-to-event end points were analyzed with the use of a Cox proportional-hazards regression model including terms for (pooled) center and treatment; pooling was performed to account for study centers that recruited fewer than four patients. P values were calculated with the use of the Wald chi-square statistic. Kaplan–Meier plots were constructed, and log-rank tests were also performed.

Number-of-event end points were compared between study groups with the use of Poisson regression with correction for overdispersion and adjustment for treatment exposure. To allow for a clear distinction between events, individual episodes of exacerbations had to be separated by a gap of at least 7 days.

In keeping with the design of the study, exacerbations were not systematically followed up after a patient's premature discontinuation of the trial medication.[17] Hence, in the efficacy analysis, only exacerbations with onset during the time a patient was receiving treatment were included.[7,20] Patients who withdrew from the trial prematurely without having had an exacerbation were considered as having had no exacerbation, and in the time-to-event analysis, their data were censored at the time of withdrawal. In the analyses of secondary end points, no corrections for multiple testing have been made.

Subgroup analyses were performed for time-to-event end points and for number-of-event end points with the use of the models described above, with additional terms for subgroups and for interactions of subgroups with the study treatment. A post hoc subgroup analysis was performed according to patients who received inhaled glucocorticoids on a consistent basis during the study treatment period versus patients who received no inhaled glucocorticoids during the treatment period. Incidence rates of serious adverse events were calculated as the number of patients with events divided by the time at risk. The rate of death from any cause was analyzed with the use of Cox regression, with treatment as a covariate. A Kaplan–Meier analysis was also performed.

RESULTS

PATIENTS

Patients were enrolled between January 2008 and April 2009. A total of 7384 patients underwent randomization, and 7376 patients (3707 in the tiotropium group and 3669 in the salmeterol group) received at least one dose of the study medication (Fig. 1). The baseline characteristics of the patients, including coexisting conditions, were balanced between the treatment groups (Table 1, and Section 11 in the Supplementary Appendix). Fewer patients in the tiotropium group than in the salmeterol group withdrew from the study prematurely: 585 patients (15.8%) vs. 648 patients (17.7%) (hazard ratio with tiotropium, 0.88; 95% confidence interval [CI], 0.78 to 0.98; P=0.02). The Kaplan–Meier plot for the time to the discontinuation of treatment is shown in Figure 2A. The collection of vital status up to day 360 was complete for 99.1% of the patients.

EXACERBATIONS

There were 4411 individual episodes of exacerbation among 2691 patients; 44% of the patients with an exacerbation had moderate COPD at the trial onset (stage II COPD, according to the classification of the Global Initiative for Chronic Obstructive Lung Disease [GOLD],[1] which specifies four stages of COPD ranging from stage I, indicating mild disease, to stage IV, indicating very severe disease). The time to the first exacerbation (the primary end point) was increased by 42 days with tiotropium as compared with salmeterol (187 days vs. 145 days, representing the time until at least 25% of the patients [first quartile] had a first exacerbation), corresponding to a 17% reduction in risk with tiotropium (hazard ratio, 0.83; 95% CI, 0.77 to 0.90; P<0.001). Figure 2B shows the Kaplan–Meier plot for the time to the first exacerbation. Given the fact that less than 50% of the patients had an exacerbation (2691 of

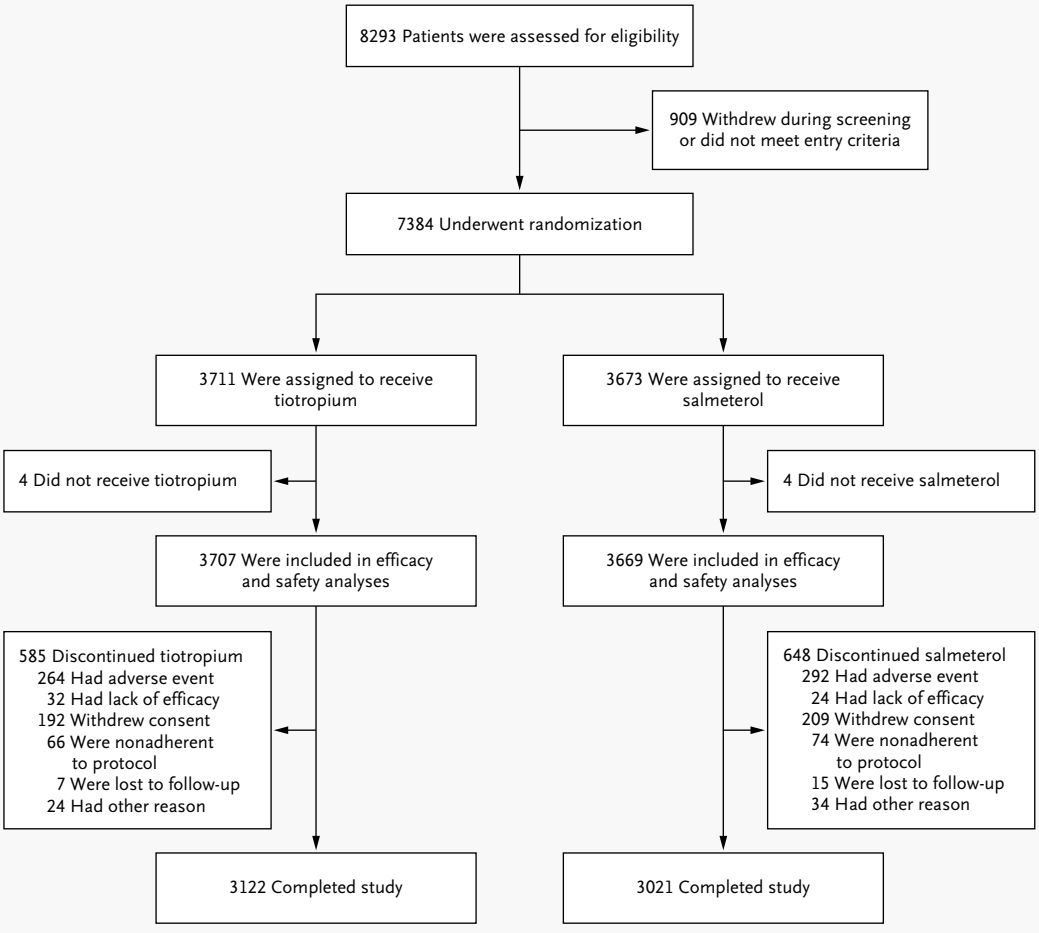


Figure 1. Screening, Randomization, and Follow-up.

7376 patients [36.5%]), it was not possible to calculate the median time to the first exacerbation; therefore, the time to the first exacerbation in the first quartile of patients was calculated instead.

Tiotropium as compared with salmeterol significantly reduced the risk of moderate exacerbations by 14% (hazard ratio, 0.86; 95% CI, 0.79 to 0.93; P<0.001) and of severe exacerbations by 28% (hazard ratio, 0.72; 95% CI, 0.61 to 0.85; P<0.001). The Kaplan–Meier plot for the time to a first severe exacerbation is shown in Figure 2C. In addition, tiotropium reduced the risk of exacerbations leading to treatment with systemic glucocorticoids by 23% (hazard ratio, 0.77; 95% CI, 0.69 to 0.85; P<0.001), exacerbations leading to treatment with antibiotics by 15% (hazard ratio, 0.85; 95% CI, 0.78 to 0.92; P<0.001), and exacerbations leading to treatment with both systemic glucocorticoids and antibiotics by 24% (hazard ratio, 0.76; 95% CI, 0.68 to 0.86; P<0.001) (Section 3 in the Supplementary Appendix).

The annual rate of exacerbations was 0.64 in the tiotropium group and 0.72 in the salmeterol group, corresponding to an 11% reduction in the rate of exacerbations with tiotropium (rate ratio, 0.89; 95% CI, 0.83 to 0.96; P=0.002). Treatment with tiotropium significantly reduced the annual rate of moderate exacerbations by 7% (0.54 vs. 0.59; rate ratio, 0.93; 95% CI, 0.86 to 1.00; P=0.048) and the annual rate of severe exacerbations by 27% (0.09 vs. 0.13; rate ratio, 0.73; 95% CI, 0.66 to 0.82; P<0.001) (Section 3 in the Supplementary Appendix). In addition, tiotropium reduced the rate of exacerbations leading to treatment with systemic glucocorticoids by 18% (0.33 vs. 0.41; rate ratio, 0.82; 95% CI, 0.76 to 0.90;

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Tiotropium (N=3707)	Salmeterol (N=3669)
Male sex (%)	74.4	74.9
Age (yr)	62.9±9.0	62.8±9.0
Smoking status		
Current smoker (%)	48.0	48.3
Smoking history (pack-yr)	38.8±20.0	37.8±19.2
Duration of COPD (yr)†	8.0±6.7	7.9±6.5
GOLD stage (%)‡		
II	47.8	49.6
III	43.1	42.1
IV	8.9	7.9
Spirometry after bronchodilation§		
FEV_1 (liters)	1.41±0.47	1.41±0.45
FEV_1 (% of predicted value)	49.2±13.3	49.4±13.1
FVC (liters)	2.71±0.81	2.75±0.82
Ratio of FEV_1 to FVC (%)	52.5±10.8	52.4±11.2
Pulmonary medications (%)		
Any	90.0	89.9
Anticholinergic drug		
Tiotropium	30.5	30.3
Short-acting	29.3	29.6
β_2-Agonists		
Long-acting¶	51.5	51.5
Short-acting	52.5	53.4
Glucocorticoids		
Inhaled¶	53.6	53.3
With tiotropium	18.7	18.2
With long-acting β_2-agonists	43.3	43.5
Oral	2.4	2.3
Methylxanthines	23.0	21.2

* Plus–minus values are means ±SD. COPD denotes chronic obstructive pulmonary disease, FEV_1 forced expiratory volume in 1 second, and FVC forced vital capacity.
† Data on duration of COPD were missing for 15 patients in the tiotropium group and 5 in the salmeterol group.
‡ The severity of COPD was defined according to the classification of the Global Initiative for Chronic Obstructive Lung Disease (GOLD), which specifies four stages of COPD ranging from stage I, indicating mild disease, to stage IV, indicating very severe disease. There were 23 patients with GOLD stage I COPD — 0.2% of the patients in the tiotropium group and 0.4% in the salmeterol group.
§ Pulmonary function testing was performed at the screening visit (visit 1). Data on FVC were missing for 1 patient in the tiotropium group.
¶ This medication was used either alone or in a fixed combination.

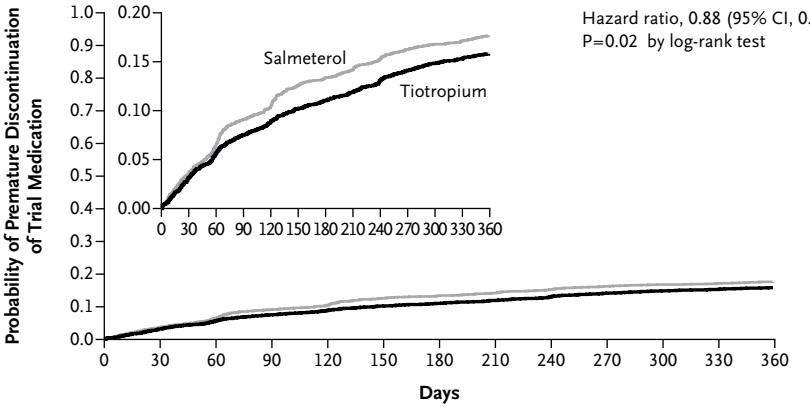
Figure 2 (facing page). Kaplan–Meier Curves for the Primary and Selected Secondary Outcomes.

Kaplan–Meier curves are shown for the probability of premature discontinuation of the study medication (Panel A), the probability of a first exacerbation of chronic obstructive pulmonary disease (COPD) (Panel B), and the probability of a first severe exacerbation of COPD leading to hospitalization (Panel C) in the tiotropium and salmeterol groups. The hazard ratios are based on a Cox proportional-hazards regression model including terms for (pooled) center and treatment. CI denotes confidence interval.

P<0.001), exacerbations leading to treatment with antibiotics by 10% (0.53 vs. 0.59; rate ratio, 0.90; 95% CI, 0.84 to 0.97; P=0.004), and exacerbations leading to treatment with both systemic glucocorticoids and antibiotics by 20% (0.23 vs. 0.28; rate ratio, 0.80; 95% CI, 0.73 to 0.88; P<0.001) (Section 3 in the Supplementary Appendix).

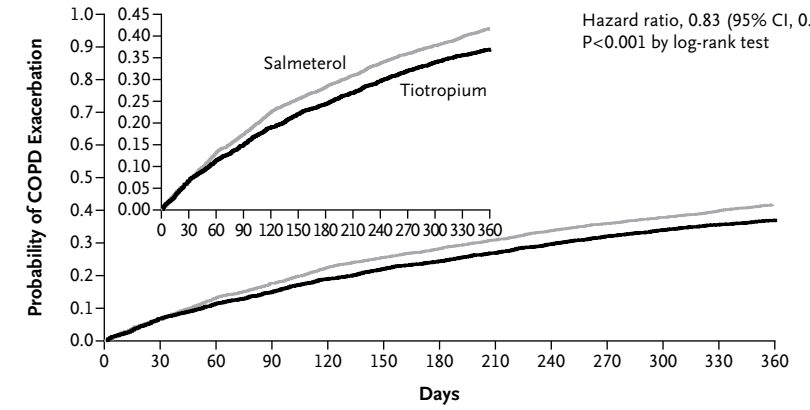
The effects of tiotropium as compared with salmeterol on the time to a first exacerbation and the annual rate of exacerbations per patient were consistent across prespecified subgroups according to age, sex, smoking status (current vs. noncurrent smoker), severity of COPD (GOLD stage), body-mass index, and use or no use of inhaled glucocorticoids at baseline (Fig. 3, and Section 4 in the Supplementary Appendix). Patients with a low body-mass index or very severe COPD seemed to benefit most from tiotropium therapy (Fig. 3). However, the P values for the tests of an interaction between treatment effect and subgroup were 0.17 for the subgroup according to body-mass index and 0.05 for the subgroup according to GOLD stage. In a post hoc analysis, a similar reduction in the risk of an exacerbation with tiotropium as compared with salmeterol was observed among the 2932 patients who used concomitant inhaled glucocorticoids during the study-treatment period (hazard ratio, 0.91; 95% CI, 0.82 to 1.02), as well as among the 4046 patients who did not use inhaled glucocorticoids at any time during the study-treatment period (hazard ratio, 0.81; 95% CI, 0.72 to 0.91). In a subgroup analysis of patients who were receiving inhaled glucocorticoids at baseline but did not receive them during the study-treatment period versus patients who were receiving inhaled glucocorticoids at baseline and continued to receive them during the study-treatment period, the annual exacerbation rate in the tiotropium group was 0.67 (95% CI, 0.57 to 0.79) among the 395 patients who discontinued the use of inhaled glucocorticoids, as compared with 0.78 (95% CI, 0.73 to 0.85) among the 1452

A



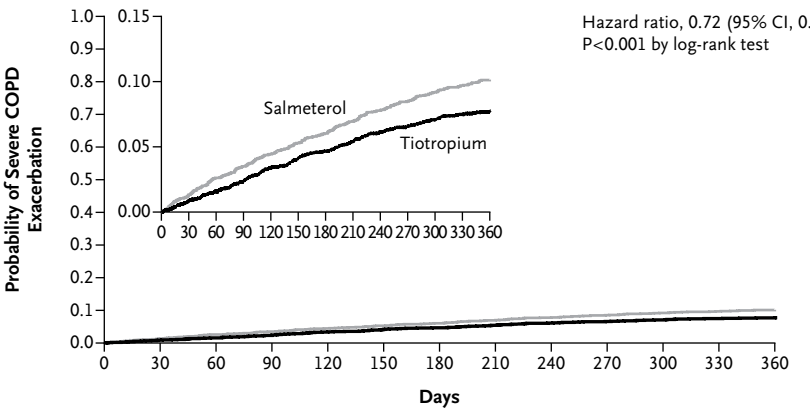
No. at Risk													
Tiotropium	3707	3592	3501	3429	3382	3330	3299	3268	3225	3186	3158	3138	2841
Salmeterol	3669	3541	3436	3337	3291	3209	3181	3151	3111	3074	3054	3037	2703

B



No. at Risk													
Tiotropium	3707	3369	3136	2955	2787	2647	2561	2455	2343	2242	2169	2107	1869
Salmeterol	3669	3328	3028	2802	2605	2457	2351	2251	2137	2050	1982	1915	1657

C



No. at Risk													
Tiotropium	3707	3564	3453	3359	3285	3217	3177	3125	3066	3017	2977	2948	2663
Salmeterol	3669	3502	3362	3244	3172	3080	3032	2982	2921	2870	2834	2806	2489

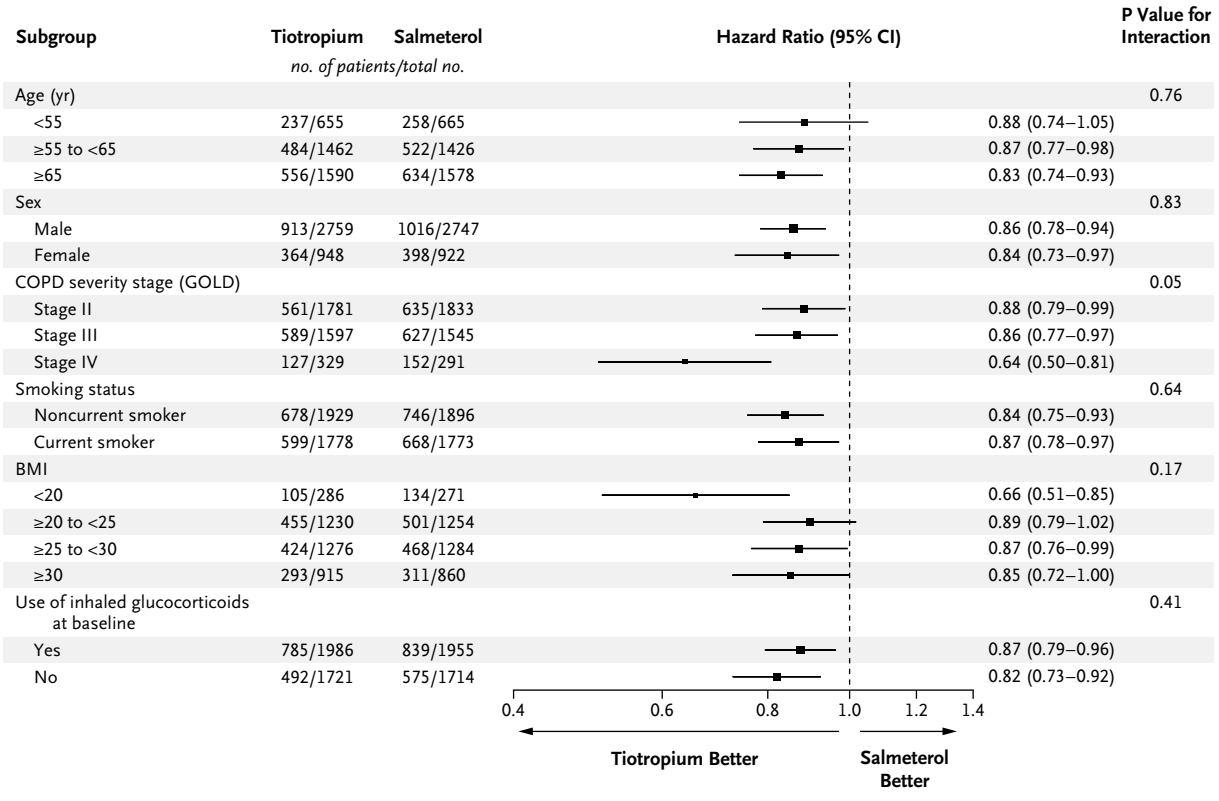


Figure 3. Subgroup Analysis of the Primary End Point.

The number of patients who had at least one exacerbation of chronic obstructive pulmonary disease (COPD) with onset during the study-treatment period is shown according to subgroup. Hazard ratios were calculated with the use of Cox regression with terms for treatment. Horizontal lines represent 95% confidence intervals. The size of the squares is proportional to the size of the subgroup. The severity of COPD was defined according to the classification of the Global Initiative for Chronic Obstructive Lung Disease (GOLD), which specifies four stages of COPD ranging from stage I, indicating mild disease, to stage IV, indicating very severe disease. Noncurrent smokers included former smokers and one person who had never smoked. The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

patients who continued to receive them; the annual exacerbation rate in the salmeterol group was 0.86 (95% CI, 0.74 to 0.99) among the 416 patients who discontinued the use of inhaled glucocorticoids, as compared with 0.81 (95% CI, 0.75 to 0.88) among the 1401 patients who continued to receive them.

SAFETY

A total of 545 patients (14.7%) in the tiotropium group and 606 (16.5%) in the salmeterol group reported a serious adverse event during the study-treatment period (Table 2). The most common serious adverse event with a frequency of 0.5% or greater was an exacerbation of COPD, which occurred in 270 patients (7.3%) in the tiotropium group and in 335 (9.1%) in the salmeterol group (Section 12 in the Supplementary Appendix).

A total of 180 cases of pneumonia were reported, of which 158 (87.8%) were radiologically confirmed (70 in the tiotropium group and 88 in the salmeterol group). There were more patients with at least one radiologically confirmed episode of pneumonia among those who received concomitant medication with inhaled glucocorticoids for at least 1 day during the study-treatment period than among those who received no inhaled glucocorticoid during the study-treatment period — 89 of 3330 patients (2.7%), of whom 72 required hospitalization, as compared with 59 of 4046 patients (1.5%), of whom 46 required hospitalization.

Table 2. Incidence Rates of Serious Adverse Events, According to System Organ Class.*

Serious Adverse Events	Tiotropium (N=3707)		Salmeterol (N=3669)		Rate Ratio for Tiotropium vs. Salmeterol (95% CI)
	no. (%)	*rate/100 patient-yr*	*no. (%)*	*rate/100 patient-yr*	
Respiratory, thoracic, and mediastinal events	300 (8.1)	8.66	366 (10.0)	10.99	0.79 (0.68–0.92)
Infections	96 (2.6)	2.69	109 (3.0)	3.15	0.85 (0.65–1.12)
Cardiac events	98 (2.6)	2.73	85 (2.3)	2.44	1.12 (0.84–1.50)
Neoplasms	51 (1.4)	1.42	43 (1.2)	1.23	1.15 (0.77–1.73)
Vascular events	37 (1.0)	1.03	25 (0.7)	0.71	1.44 (0.87–2.39)
Gastrointestinal events	32 (0.9)	0.89	32 (0.9)	0.92	0.97 (0.59–1.58)
Nervous system events	28 (0.8)	0.78	29 (0.8)	0.83	0.94 (0.56–1.58)
General events†	16 (0.4)	0.44	27 (0.7)	0.77	0.57 (0.31–1.07)
Injury, poisoning, and procedural complications	22 (0.6)	0.61	19 (0.5)	0.54	1.13 (0.61–2.08)
Musculoskeletal and connective-tissue events	10 (0.3)	0.28	22 (0.6)	0.63	0.44 (0.21–0.93)

* Listed are incidence rates per 100 patient-years and incidence rate ratios of serious adverse events that occurred from the beginning of the study-treatment period until 30 days after the last dose of study drug was received and that were reported by at least 0.5% of the patients in either study group. The adverse events are categorized according to the system organ classes in the *Medical Dictionary for Regulatory Activities*.

† This category includes the diagnostic terms "death" and "sudden death."

There were 142 deaths during the planned treatment period of 360 days (including deaths among patients who had withdrawn from the study prematurely and whose vital status was recorded at 360 days): 64 in the tiotropium group and 78 in the salmeterol group (hazard ratio with tiotropium, 0.81; 95% CI, 0.58 to 1.13). Additional information is provided in Section 13 in the Supplementary Appendix.

DISCUSSION

Tiotropium, as compared with salmeterol, significantly increased the time to the first moderate or severe exacerbation of COPD and significantly decreased the annual rate of exacerbations among patients with moderate-to-very-severe COPD. The benefit with tiotropium was seen consistently in all the major subgroups that were considered in this trial and was independent of the concomitant use of inhaled glucocorticoids.

This 1-year study was designed and powered for the end point of moderate and severe exacerbations, one of the most relevant patient-related outcomes, with important effects on patients' families, caregivers, health care providers, and payers.[4-6] Any exacerbation that can be avoided would be beneficial from the perspective of both the patient and the health care system and constitutes a major treatment goal in COPD.[1,2]

Previous large, long-term trials have shown that both salmeterol and tiotropium reduce the rate of exacerbations.[8,12] However, to date, there has been insufficient evidence from direct comparisons of the two drugs; therefore, current guidelines do not favor one long-acting agent over the other for patients with COPD.[1,2]

The Kaplan–Meier analyses of the time to the first exacerbation show that the benefit with tiotropium as compared with salmeterol became evident as early as approximately 1 month after the initiation of treatment and was maintained over the entire 1-year study period. Thus, it appears to be unlikely that the difference in favor of tiotropium was due to early discontinuation of treatment among patients in the salmeterol group who did not have a response to that drug. Tiotropium and salmeterol have been shown to reduce airflow limitation and hyperinflation but may also directly or indirectly have an effect on various aspects of lung inflammation.[21,22] However, the relevance of these mechanisms to the observed differences in the end points related to exacerbations remains to be determined. Whether the

observed differences might be due to differences in the aerosolizing systems, the particle size of the aerosols, or the distribution of the drug in the lung is also unknown.

The annual exacerbation rates in this study were lower than those in large trials involving patients with COPD, such as the Trial of Inhaled Steroids and Long-acting β_2 Agonists (TRISTAN)[23] and the Towards a Revolution in COPD Health trial (TORCH; ClinicalTrials.gov number, NCT00268216),[8] were similar to those in the Understanding Potential Long-Term Impacts on Function with Tiotropium trial (UPLIFT, NCT00144339),[12] and were higher than those in a recent 1-year study comparing the efficacy of two long-acting β_2-agonists.[24] This variability may reflect differences in inclusion criteria and in the concomitant medications, such as inhaled glucocorticoids, that patients were allowed to receive. In our trial, consistent with current guideline recommendations, concomitant therapy with inhaled glucocorticoids was allowed but was not mandatory, because the patient population included a substantial proportion of patients with moderate COPD (GOLD stage II). Approximately 40% of the patients received concomitant therapy with inhaled glucocorticoids on a consistent basis during the study-treatment period. In a post hoc analysis, treatment with tiotropium decreased the risk of exacerbations more than did treatment with salmeterol both in patients who were receiving inhaled glucocorticoids and in those who were not receiving them, suggesting that the benefit of tiotropium was independent of the use of inhaled glucocorticoids.

In addition, the rate of exacerbations among patients in the tiotropium group who were receiving inhaled glucocorticoids at baseline but did not continue receiving them during the study-treatment period was not higher than the rate among those who were receiving inhaled glucocorticoids at baseline and continued to receive them during the study-treatment period. This finding is consistent with the results of the COPD and Seretide: a Multi-Center Intervention and Characterization (COSMIC) study, which showed that withdrawal of fluticasone for 1 year after a 3-month run-in period with a fixed combination of fluticasone and salmeterol was not associated with an increase in moderate or severe exacerbations.[25]

Differences between study groups in the proportion of patients discontinuing the study treatment have been seen in other studies involving patients with COPD and are most often attributed to relative differences in the efficacy, safety, or both of the agents used in the study.[7,12,26,27] Similarly, we observed a significantly higher rate of premature discontinuation of treatment in the salmeterol group than in the tiotropium group. However, as compared with the between-group differences that have been seen in placebo-controlled studies, the absolute difference was quite small (1.9 percentage points).

Both tiotropium and salmeterol have safety profiles that have been well described in the literature.[28-31] Overall, the incidence of serious adverse events, adverse events leading to treatment discontinuation, and fatal events were similar across treatments.

In summary, among patients with moderate-to-very-severe COPD and a history of exacerbation, tiotropium was more effective than salmeterol in all the exacerbation end points that were assessed and across all major subgroups. The results of this large trial provide data on which to base the choice of long-acting bronchodilator therapy for maintenance treatment of COPD.

Dr. Vogelmeier reports receiving consulting fees and travel support from Boehringer Ingelheim, payment for board membership from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Mundipharma, Novartis, and Nycomed, fees for expert testimony and grant support from Talecris Biotherapeutics, and lecture fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Merck, Novartis, Nycomed, and Talecris Biotherapeutics; Dr. Hederer, being formerly employed by Boehringer Ingelheim; Drs. Glaab and Schmidt, being currently employed by Boehringer Ingelheim; Dr. Rutten-van Mölken, receiving grant support from Boehringer Ingelheim and having consulting fees, travel support, and fees for participation in review activities from Boehringer Ingelheim paid to her institution on her behalf; Dr. Beeh, having consulting fees or honoraria, grant support, and payments for development of educational materials from Boehringer Ingelheim and grant support from Almirall, Novartis, Mundipharma, Cytos Biotechnology, GlaxoSmithKline, Pfizer, and Revotar Biopharmaceuticals paid to his institution on his behalf; Dr. Rabe, receiving consulting fees and honoraria and payment for board membership from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Merck, Novartis, Nycomed, and Pfizer and grant support from Altana, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Roche; and Dr. Fabbri, receiving travel support from Boehringer Ingelheim, consulting fees from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Merck, Novartis, Nycomed, Pfizer, and Sigma-Tau Pharmaceuticals, and lecture fees from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Merck, Novartis, Nycomed, and Pfizer and having grant support from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Menarini, Merck, Nycomed, Pfizer, Schering-Plough (now Merck), Sigma-Tau Pharmaceuticals, and Union Chimique Belge paid to his institution on his behalf. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients who participated in the trial; Dr. Klaus Fichtner, Vera Drews, and Nicole Bader for administrative trial support; Dr. Steven Kesten, Dr. Fee Rühmkorf, Dr. Harald Kögler, Dr. Susanne Stowasser, Dr. Brigitta Monz, and Dagmar Selim for scientific advice; Dr. Inge Leimer and Achim Müller for statistical advice; Michael Betke-Hornfeck for technical trial support; Christine Meissner and Christina Raabe for data management support; Bernd Damian and Rafal Falkowski for programming support; Dr. Silke Wienecke, Declan Tobin, and Karen Ryan from Parexel for onsite monitoring and site management support; Natalie Barker and Claire Scarborough, from Parexel MedCom, for editorial and technical support in the preparation of the manuscript; and Dr. Franklin Cerasoli, Dr. Idelle Weisman, and Dr. Lalitha Aiyer for review of the manuscript.

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