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A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease

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ABSTRACT

BACKGROUND

Previous studies showing that tiotropium improves multiple end points in patients with chronic obstructive pulmonary disease (COPD) led us to examine the long-term effects of tiotropium therapy.

METHODS

In this randomized, double-blind trial, we compared 4 years of therapy with either tiotropium or placebo in patients with COPD who were permitted to use all respiratory medications except inhaled anticholinergic drugs. The patients were at least 40 years of age, with a forced expiratory volume in 1 second (FEV₁) of 70% or less after bronchodilation and a ratio of FEV₁ to forced vital capacity (FVC) of 70% or less. Coprimary end points were the rate of decline in the mean FEV₁ before and after bronchodilation beginning on day 30. Secondary end points included measures of FVC, changes in response on St. George's Respiratory Questionnaire (SGRQ), exacerbations of COPD, and mortality.

RESULTS

Of a total of 5993 patients (mean age, 65±8 years) with a mean FEV₁ of 1.32±0.44 liters after bronchodilation (48% of predicted value), we randomly assigned 2987 to the tiotropium group and 3006 to the placebo group. Mean absolute improvements in FEV₁ in the tiotropium group were maintained throughout the trial (ranging from 87 to 103 ml before bronchodilation and from 47 to 65 ml after bronchodilation), as compared with the placebo group (P<0.001). After day 30, the differences between the two groups in the rate of decline in the mean FEV₁ before and after bronchodilation were not significant. The mean absolute total score on the SGRQ was improved (lower) in the tiotropium group, as compared with the placebo group, at each time point throughout the 4-year period (ranging from 2.3 to 3.3 units, P<0.001). At 4 years and 30 days, tiotropium was associated with a reduction in the risks of exacerbations, related hospitalizations, and respiratory failure.

CONCLUSIONS

In patients with COPD, therapy with tiotropium was associated with improvements in lung function, quality of life, and exacerbations during a 4-year period but did not significantly reduce the rate of decline in FEV₁. (ClinicalTrials.gov number, NCT00144339.)

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PROSPECTIVE STUDIES TESTING EFFECTS on the progression of chronic obstructive pulmonary disease (COPD) through the evaluation of the slope of the forced expiratory volume in 1 second (FEV₁) have not shown that inhaled short-acting anticholinergic drugs, inhaled corticosteroids, or *N*-acetylcysteine alter this marker of disease progression.¹⁻⁷ To date, only smoking cessation has prospectively been shown to alter the rate of decline of FEV₁ in patients with COPD.²

Tiotropium is a once-daily, inhaled anticholinergic drug that provides at least 24-hour improvements in airflow and hyperinflation in patients with COPD.⁸⁻¹⁰ Clinical trials lasting 6 weeks to 12 months have shown improvements in exercise tolerance, health-related quality of life, and rates of dyspnea and exacerbations.⁸⁻¹³ A retrospective analysis of 1-year, placebo-controlled trials indicated that tiotropium had the potential to slow the rate of decline in FEV₁.¹⁴

Given previous favorable clinical outcomes, we designed this trial to prospectively extend these observations to 4 years.¹⁵ In the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial, we tested whether tiotropium would reduce the rate of decline in FEV₁ in patients with COPD who were permitted therapy other than other inhaled anticholinergic drugs, according to current COPD guidelines. We evaluated the long-term effects of tiotropium therapy on the clinically important outcomes of health-related quality of life, exacerbations, related hospitalizations, and mortality.

METHODS

STUDY DESIGN

Details of the study design were reported previously by Decramer et al.¹⁵ and are summarized below. The protocol is provided in Supplementary Appendix 2, available with the full text of this article at www.nejm.org.

The study was a 4-year, randomized, double-blind, placebo-controlled, parallel-group trial involving patients with moderate-to-very-severe COPD.¹⁵ The two coprimary end points were the yearly rate of decline in the mean FEV₁ before the use of a study drug and short-acting bronchodilators in the morning (prebronchodilator) and after the use of a study drug (postbronchodilator) from day 30 (steady state) until completion of double-blind treatment. Secondary outcome measures included the rate of decline in the mean

forced vital capacity (FVC) and slow vital capacity (SVC); health-related quality of life, as measured by the total score on St. George's Respiratory Questionnaire (SGRQ), in which scores range from 0 to 100, with lower scores indicating improvement and a change of 4 units or more considered to be clinically meaningful; exacerbations of COPD (as defined below) and related hospitalizations; and the rate of death from any cause and from lower respiratory conditions. Details regarding secondary end points are provided in Supplementary Appendix 3.

Patients received either 18 μg of tiotropium or a matching placebo once daily, delivered through the HandiHaler inhalation device (Boehringer Ingelheim). All respiratory medications, except other inhaled anticholinergic drugs, were permitted during the trial. Smoking cessation programs were offered to all patients before randomization, and self-reported smoking behavior was recorded at each visit. At the end of the study, all patients were provided with and asked to take 40 μg of ipratropium (two inhaler actuations) four times daily and to return for a final assessment 30 days later.

PATIENTS

Patients were recruited at 490 investigational centers in 37 countries. Criteria for participation included a diagnosis of COPD, an age of 40 years or more, a smoking history of at least 10 pack-years, a postbronchodilator FEV₁ of 70% or less of the predicted value, and an FEV₁ of 70% or less of the FVC (after supervised administration of 80 μg of ipratropium [four actuations], followed by 400 μg of albuterol [four actuations] 60 minutes later).¹⁶ Key exclusion criteria were a history of asthma, a COPD exacerbation or respiratory infection within 4 weeks before screening, a history of pulmonary resection, use of supplemental oxygen for more than 12 hours per day, and the presence of a coexisting illness that could preclude participation in the study or interfere with the study results. The protocol was approved by the ethics committee at each center, and all patients provided written informed consent.

PROCEDURES

After a screening period, eligible patients were randomly assigned in a 1:1 ratio to receive either tiotropium or placebo with the use of centralized randomization in blocks of four, stratified according to site. After randomization, clinic visits oc-

curred at 1 month and 3 months and then every 3 months throughout the 4-year study period.

Spirometry was performed according to American Thoracic Society guidelines¹⁷ at randomization, at the 1-month visit, at visits every 6 months throughout the study period, and at a follow-up visit approximately 30 days after the end of the study. Before spirometry testing, respiratory medications were withheld according to the following schedule: study drug, 24 hours; morning dose of inhaled corticosteroids, 12 hours; short-acting beta-agonists, 8 hours; short-acting (twice-daily or four-times-daily) theophyllines and long-acting beta-agonists (including fixed combination with inhaled corticosteroids), 24 hours; and once-daily theophyllines, 48 hours. Prebronchodilator spirometry was performed initially, followed immediately by the blinded administration of a study drug. Immediately thereafter, all patients received 80 μg of ipratropium (four inhaler actuations), followed 60 minutes later by 400 μg of albuterol (four inhaler actuations). Thirty minutes after the administration of albuterol, spirometry was again performed. Sites were provided with identical spirometry equipment and study-specific software. A centralized quality-assurance review of all spirometry data was performed during the study.¹⁵

Health-related quality of life was measured with the use of the SGRQ before prebronchodilator spirometry testing at baseline and every 6 months.¹⁸ Reports of adverse events were collected at each visit.

Exacerbations were defined as an increase in or the new onset of more than one respiratory symptom (cough, sputum, sputum purulence, wheezing, or dyspnea) lasting 3 days or more and requiring treatment with an antibiotic or a systemic corticosteroid. Data regarding exacerbations and related hospitalizations were collected on study-specific case-report forms at every visit. An independent data and safety monitoring committee reviewed data throughout the trial (for details, see Supplementary Appendixes 2 and 4).

STUDY OVERSIGHT

The design of the trial, the monitoring of the trial conduct, the approval of the statistical analyses, the review and interpretation of the data, the writing of the manuscript, and the decision to publish the manuscript involved a joint advisory committee composed of four academic researchers (three investigators and a statistician), three researchers employed by Boehringer Ingelheim,

and a representative of Pfizer (see Supplementary Appendix 4). The first draft of the manuscript was written by an academic investigator, and the final content of the manuscript was developed collaboratively by all authors. Statistical analyses were performed by employees of Boehringer Ingelheim. All authors had full access to the data and vouch for the accuracy and completeness of the data and the analyses.

STATISTICAL ANALYSIS

The number of patients needed for the study was based on the assumption of a standard deviation of 90 ml in the rate of decline in the mean FEV₁ during the 4-year period² to detect a difference of 15 ml between the tiotropium group and the placebo group, with a power of more than 90% at a significance level of 5% with the use of a two-sided test. The sample size was also based on an assumption that it would not be possible to perform a complete evaluation of 35% of patients because of early discontinuation. The sample size was chosen to be sufficiently large to undertake subgroup analyses of the primary end point in smokers, who were assumed to comprise about 40% of enrolled patients. The other planned subgroup analyses included the variables of age, sex, severity of COPD, region, reversibility, body-mass index, and concomitant use of medication. In addition, we conducted a post hoc subgroup analysis comparing patients in each study group who were or were not receiving inhaled corticosteroids or long-acting beta-agonists at baseline.

The two coprimary end points were analyzed with the use of a normal random-effects model in which the mean FEV₁ changed linearly after day 30 for each patient, the intercepts and slopes among patients were assumed to be random with an arbitrary covariance matrix, and the treatment effect was fixed.¹⁹ The same model was used for the secondary end points of FVC and SVC (from day 30 until study completion) and the total score on the SGRQ (from 6 months until study completion). All patients who underwent randomization and received a study drug and who had at least three post-randomization data points (at least two for the SGRQ) were included in the analyses. We used likelihood-based methods to handle missing data for the random coefficient regression analysis, and therefore no imputation was deemed necessary. A sensitivity analysis was conducted for the rate of decline in the mean FEV₁, with adjustment for baseline FEV₁, smoking

status, age, sex, and height. Analyses of heterogeneity of subgroups were assessed by testing for interaction between study-group slope and each baseline factor. The yearly rates of decline from baseline to 30 days after the discontinuation of a study drug were analyzed using the Wilcoxon rank-sum test. The mean effects at various visits were compared in the two study groups with the use of repeated-measures analysis of covariance without imputation of missing values. SGRQ data from Turkey were excluded owing to incorrect validation of the questionnaire.

The times to the first exacerbation and associated hospitalization in the two study groups were compared with the use of log-rank tests and were prespecified as the key secondary analyses. Cox regression was used to derive hazard ratios. Kaplan-Meier curves of the probability of no exacerbation and related hospitalization were calculated. The number of events and event days were compared between study groups with the use of Poisson regression with correction for treatment exposure and overdispersion.²⁰

All patients who received a study drug were included in the analysis of safety and discontinuations. Incidence rates were computed as the number of patients with events divided by the time at risk. Time-to-event analyses were performed with the use of the log-rank test; hazard ratios were calculated with the use of Cox regression.

Analyses were performed with the use of SAS software, version 8.2 (SAS Institute). All reported P values are two-sided and were not adjusted for multiple testing. The scientific steering committee (Joint Advisory Committee) added a number of secondary end points and updated the analyses during the course of the trial while its members were unaware of study-group assignments. Details of the statistical analysis plan are provided in Supplementary Appendix 3.

RESULTS

STUDY POPULATION

Patients were recruited from January 2003 through March 2004; the study ended in February 2008. Of the 8020 patients who were recruited, 5993 underwent randomization (Fig. 1). Of these patients, 4383 (73%) completed 2 years, 3891 (65%) completed 3 years, and 3569 (60%) completed at least 45 months. The median duration of treatment was 1436 days in the tiotropium group and

1435 days in the placebo group. A higher proportion of patients did not complete at least 45 months of treatment in the placebo group (44.6%) than in the tiotropium group (36.2%, $P < 0.001$) (Fig. 2A). The majority of discontinuations were due to adverse events.

Baseline characteristics and concomitant use of respiratory medications were similar in the two study groups (Table 1). The mean age was 65 ± 8 years among the patients, of whom 75% were men and 30% were current smokers. The mean prebronchodilator FEV₁ was 1.10 ± 0.40 liters (39% of the predicted value), and the mean postbronchodilator FEV₁ was 1.32 ± 0.44 liters (48% of the predicted value). The mean increase in FEV₁ after maximal bronchodilation was $23 \pm 18\%$.²¹ Patients whose disease was classified as stage II, III, or IV, according to criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD), comprised 46%, 44%, and 9% of patients, respectively.¹ The mean baseline prebronchodilator FEV₁ was lower in patients who discontinued a study drug than in those who completed the study period (37% vs. 41% of the predicted value, $P < 0.001$). More than 90% of patients were receiving respiratory medications at baseline.

During the study period, 26% of patients changed their smoking behavior. On at least one clinic visit, 74% of patients reported having received inhaled corticosteroids, 72% long-acting beta-agonists, and 46% a fixed combination of the two.

RATE OF DECLINE IN LUNG FUNCTION

The rate of decline in the mean postbronchodilator FEV₁ was greater in patients who prematurely discontinued a study drug (55 ± 4 ml per year in the tiotropium group and 57 ± 4 ml per year in the placebo group), as compared with those who completed the study period (38 ± 1 ml per year in the tiotropium group and 40 ± 1 ml per year in the placebo group).

There were no significant differences between study groups in the rate of decline in the mean values for FEV₁ and FVC either before or after bronchodilation from day 30 to the end of study-drug treatment (Table 2; for SVC measures, see Supplementary Appendix 5). In the tiotropium group, the mean values for FEV₁ and FVC before and after bronchodilation showed significant improvements that were maintained at all time points after randomization (Fig. 2B and 2C). Mean improvements in FEV₁ in the tiotropium group,

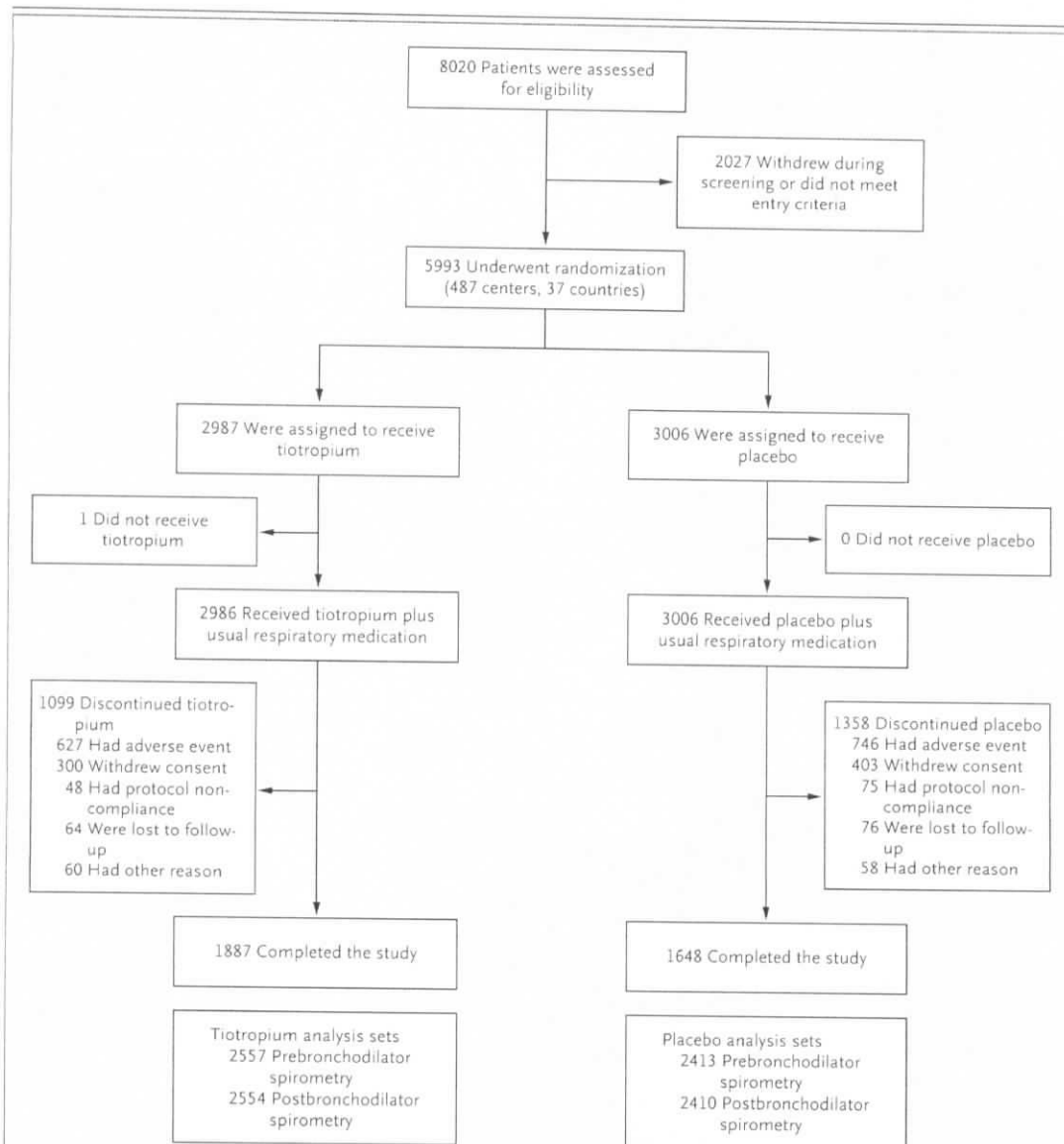


Figure 1. Enrollment and Outcomes.

Patients with three or more measurements of pulmonary function after day 30 were included in the analysis of lung function. Patients in the study were permitted to use all respiratory medications except other inhaled anticholinergic drugs. After the initial assessment, one patient underwent randomization twice.

as compared with the placebo group, ranged from 87 to 103 ml before bronchodilation and from 47 to 65 ml after bronchodilation ($P < 0.001$). Adjustments for baseline FEV₁, smoking status, age, sex, and height had similar results.

The prespecified subgroup analyses revealed no significant heterogeneity in the effect of tiotropium according to the baseline variables examined (Supplementary Appendix 6). In a post hoc analysis, between-group differences in the rate of decline in postbronchodilator FEV₁ were ob-

served in favor of tiotropium, as compared with placebo (40 ± 3 ml in the tiotropium group and 47 ± 3 in the placebo group, $P = 0.046$) in the subgroup of 1554 patients who were not receiving either inhaled corticosteroids or long-acting beta-agonists at baseline.

Among 3421 patients from baseline until 30 days after treatment discontinuation, the median rate of decline in prebronchodilator FEV₁ did not differ significantly between the tiotropium group (15 ml per year) and the placebo group (17 ml per

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Tiotropium (N=2986)	Placebo (N=3006)
Male sex (%)	75.4	73.9
Age (yr)	64.5±8.4	64.5±8.5
Body-mass index	26.0±5.1	25.9±5.1
Smoking status		
Current smoker (%)	29.3	29.9
Smoking history (pack-yr)	49.0±28.0	48.4±27.9
Duration of COPD (yr)	9.9±7.6	9.7±7.4
Baseline spirometry		
Before bronchodilation		
FEV ₁ (liters)	1.10±0.40	1.09±0.40
FEV ₁ (% of predicted value)	39.5±12.0	39.3±11.9
FVC (liters)	2.63±0.81	2.63±0.83
Ratio of FEV ₁ to FVC	42.4±10.5	42.1±10.5
After bronchodilation		
FEV ₁ (liters)	1.33±0.44	1.32±0.44
FEV ₁ (% of predicted value)	47.7±12.7	47.4±12.6
FVC (liters)	3.09±0.86	3.09±0.90
Ratio of FEV ₁ to FVC	43.6±10.8	43.3±10.7
GOLD stage (%)†		
II	46	45
III	44	44
IV	8	9
SGRQ total score (units)‡	45.7±17.0	46.0±17.2
Respiratory medication (%)		
Any	93.4	93.1
Inhaled anticholinergic§		
Short-acting	44.9	44.1
Long-acting	2.0	1.6
Inhaled β ₂ -agonist§		
Short-acting	68.5	68.1
Long-acting	60.1	60.1
Corticosteroid		
Inhaled§	61.6	61.9
Oral	8.4	8.3
Theophylline compound	28.4	28.5
Mucolytic agent	7.4	6.9
Leukotriene-receptor antagonist	3.3	3.1
Supplemental oxygen	2.3	1.9

* Plus-minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters. FEV₁ denotes forced expiratory volume in 1 second, FVC forced vital capacity, and SGRQ St. George's Respiratory Questionnaire.

† Data were missing in this category for 2% of patients. The enrollment of three patients with stage I disease, according to criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD), represented a protocol violation, but data from these patients were included in the study.

‡ Data are for 2888 patients in the tiotropium group and 2909 patients in the placebo group. Scores on the SGRQ range from 0 to 100, with lower scores indicating improvement; a change of 4 units or more is considered to be clinically meaningful.

§ This medication was used either alone or as a fixed combination.

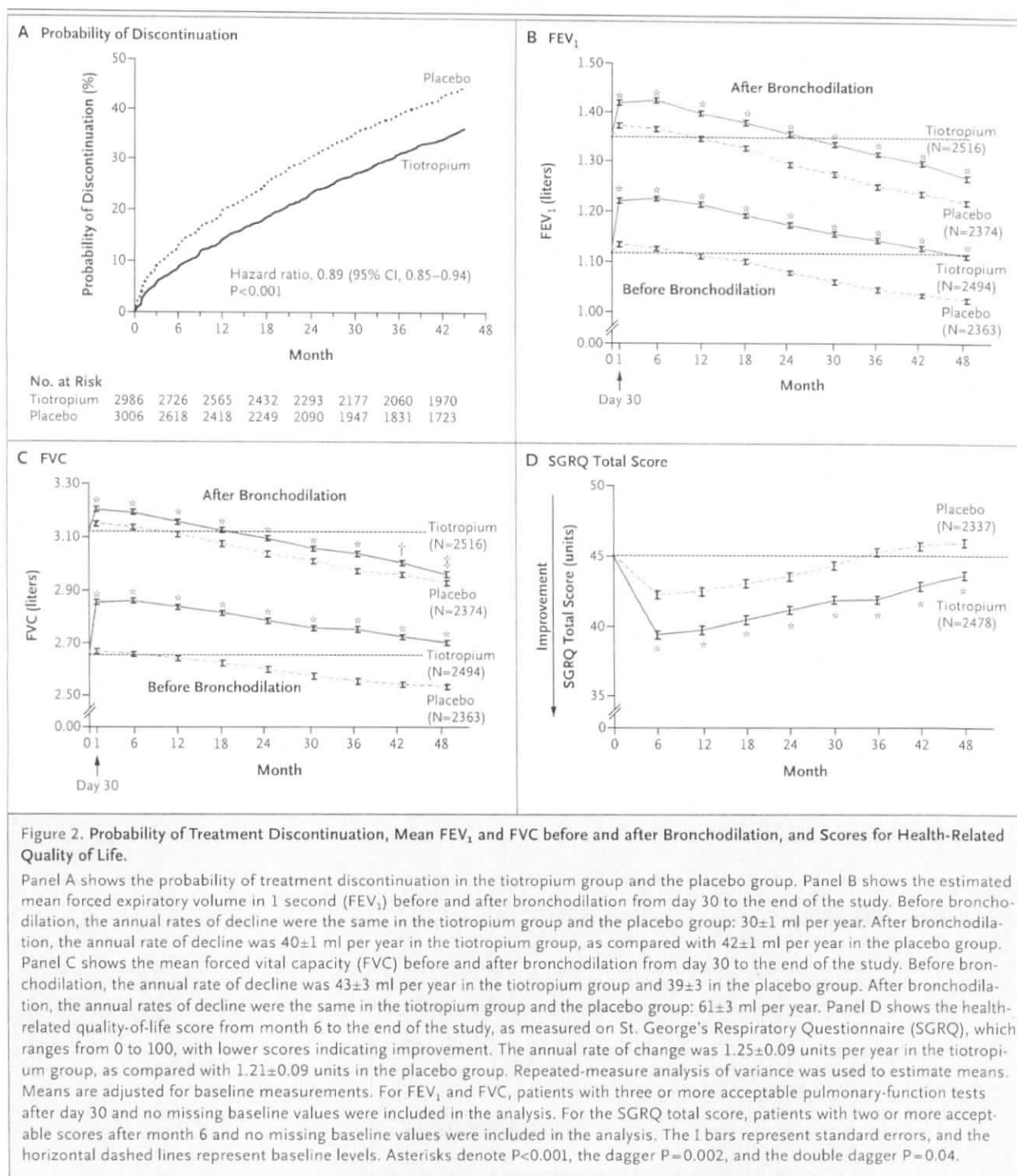


Table 2. Annual Rates of Decline in FEV₁ and FVC before and after Bronchodilation and Scores on Health-Related Quality of Life.*

Variable	Tiotropium		Placebo		Difference between Tiotropium and Placebo (95% CI)	P Value†
	Patients	Mean Decline	Patients	Mean Decline		
	no.	ml/yr	no.	ml/yr		
FEV ₁						
Before bronchodilation	2557	30±1	2413	30±1	0±2 (-4 to 4)	0.95
After bronchodilation	2554	40±1	2410	42±1	-2±2 (-6 to 2)	0.21
FVC						
Before bronchodilation	2557	43±3	2413	39±3	4±4 (-4 to 12)	0.30
After bronchodilation	2554	61±3	2410	61±3	1±4 (-7 to 9)	0.84
Total SGRQ score‡	2505	1.25±0.09	2362	1.21±0.09	0.04±0.13 (-0.2 to 0.3)	0.78

* Plus-minus values are means ±SE. Values for the rate of decline in forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) are expressed as milliliters per year. Values were measured from day 30 until the end of the study (including 30 days after the discontinuation of treatment). Patients with three or more measurements after day 30 were included in the analysis of lung function.

† P values are unadjusted.

‡ Values for the health-related quality-of-life score on St. George's Respiratory Questionnaire (SGRQ) are expressed in units per year. Scores on the SGRQ range from 0 to 100, with an increase in the score indicating a decline in quality of life; a change of 4 units or more is considered to be clinically meaningful. Patients with two or more measurements after month 6 were included in the analysis of the SGRQ.

year) ($P=0.25$). However, among 3418 patients who had technically acceptable postbronchodilator spirometry, there was a significant difference in favor of tiotropium in the median rate of decline in postbronchodilator FEV₁ (27 ml per year in the tiotropium group, as compared with 32 ml per year in the placebo group; $P=0.01$).

HEALTH-RELATED QUALITY OF LIFE

Significant differences in favor of tiotropium were observed at all time points for the mean absolute change in the SGRQ total score (ranging from 2.3 to 3.3 units, $P<0.001$), although the differences on average were below what is considered to have clinical significance (Fig. 2D). The overall mean between-group difference in the SGRQ total score at any time point was 2.7 (95% confidence interval [CI], 2.0 to 3.3) in favor of tiotropium ($P<0.001$). A higher proportion of patients in the tiotropium group than in the placebo group had an improvement of 4 units or more in the SGRQ total scores from baseline at 1 year (49% vs. 41%), 2 years (48% vs. 39%), 3 years (46% vs. 37%), and 4 years (45% vs. 36%) ($P<0.001$ for all comparisons). There were no significant between-group differences in the rate of decline in SGRQ scores from 6 months to the end of the study (Table 2).

EXACERBATIONS

Tiotropium was associated with a significant delay in the time to the first exacerbation, with a

median of 16.7 months (95% CI, 14.9 to 17.9) in the tiotropium group and 12.5 months (95% CI, 11.5 to 13.8) in the placebo group. Tiotropium was also associated with a significant delay in the time to the first hospitalization for an exacerbation. Since hospitalizations for exacerbations occurred in less than 50% of patients, a median time to the first event cannot be calculated. In the tiotropium group, the associated hazard ratios were 0.86 (95% CI, 0.81 to 0.91) and 0.86 (95% CI, 0.78 to 0.95), respectively. Tiotropium was also associated with a reduction in the mean number of exacerbations of 14% ($P<0.001$) (Fig. 3A and Supplementary Appendix 7). The mean numbers of exacerbations leading to hospitalizations were infrequent and did not differ significantly between the two study groups (Table 3).

MORTALITY

Data regarding vital status were systematically requested for patients who prematurely discontinued study participation on a recorded date determined as 4 years from the first day of administration of a study drug. Data regarding deaths extending beyond 4 years (up to and beyond 1470 days) were not systematically collected but were occasionally received. Every effort was made to ensure that vital-status data were full and complete up to 4 years, as described. Vital-status information (at least 45 months of follow-up, including patients who discontinued treatment) was known

for 98% of patients in the tiotropium group and 97% in the placebo group. During a period of 4 years plus 30 days (1470 days) included in the intention-to-treat analysis, 941 patients died: 14.9% in the tiotropium group and 16.5% in the placebo group (hazard ratio, 0.89; 95% CI, 0.79 to 1.02) (Fig. 3B). For the 4-year, protocol-defined study period up to day 1440, among patients for whom vital-status information was available, 921 patients died: 14.4% in the tiotropium group and 16.3% in the placebo group (hazard ratio, 0.87; 95% CI, 0.76 to 0.99).

ADVERSE EVENTS

Safety was monitored through the collection of reports of adverse events, serious adverse events, and fatal events while patients were receiving a study drug (including the last day of a study drug plus 30 days). Adverse events were reported by 92.6% of the tiotropium group and 92.3% of the placebo group. The proportions of serious adverse events were 51.6% in the tiotropium group and 50.2% in the placebo group. Fatal events occurred in 381 patients (12.8%) in the tiotropium group and 411 (13.7%) in the placebo group (hazard ratio, 0.84; 95% CI, 0.73 to 0.97).

In the tiotropium group, as compared with the placebo group, the most common adverse events were due to lower respiratory causes, including COPD exacerbations (64.8% and 66.1%, respectively; relative risk, 0.84; 95% CI, 0.79 to 0.89), pneumonia (14.5% and 13.9%; relative risk, 0.96; 95% CI, 0.84 to 1.10), and dyspnea (12.2% and 14.7%; relative risk, 0.75; 95% CI, 0.65 to 0.86). Respiratory failure developed in 88 patients in the tiotropium group and in 120 in the placebo group (relative risk, 0.67; 95% CI, 0.51 to 0.89). Myocardial infarction developed in 67 patients in the tiotropium group and 85 in the placebo group (relative risk, 0.73; 95% CI, 0.53 to 1.00), and stroke developed in 82 in the tiotropium group and 80 in the placebo group (relative risk, 0.95; 95% CI, 0.70 to 1.29). Adverse events consistent with the known safety profile of tiotropium, such as dry mouth and constipation, were observed.^{22,23}

Serious adverse events reported by more than 1% of patients in either study group were either cardiac or respiratory in nature (Table 4). The incidence of such serious adverse events was lower in the tiotropium group than in the placebo group, including a reduced risk of conges-

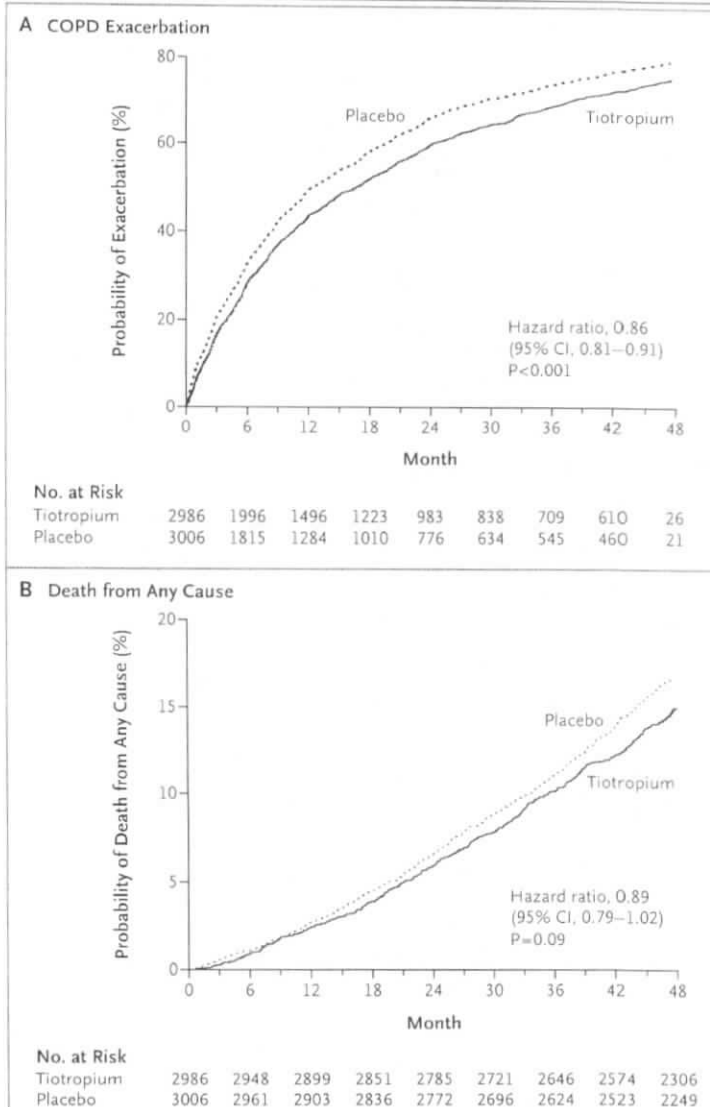


Figure 3. Kaplan–Meier Estimates of the Probability of COPD Exacerbation and Death from Any Cause.

Kaplan–Meier curves show the cumulative incidence estimate of the probability of COPD exacerbation (Panel A) and of death from any cause at day 1470 for all patients for whom data were available regarding vital status (Panel B). The numbers of patients who continued to receive a study drug (including those at 30 days after the last dose) are listed for each time point, with the study period truncated at 48 months. All patients who received at least one dose of a study drug were included in the analysis. P values were calculated with use of the log-rank test.

tive heart failure, COPD exacerbation, dyspnea, or respiratory failure. Serious adverse events according to organ system and adverse events that were reported by more than 3% of patients in either of the study groups are provided in Supplementary Appendix 8.

Table 3. Exacerbations of COPD and Related Hospitalizations.*

Variable	Tiotropium	Placebo	Relative Risk for Tiotropium vs. Placebo (95% CI)	P Value
Exacerbation†				
Per patient-year — no.	0.73±0.02	0.85±0.02	0.86 (0.81–0.91)	<0.001
Leading to hospitalization — no. per patient-year	0.15±0.01	0.16±0.01	0.94 (0.82–1.07)	0.34
Days per patient-year	12.11±0.32	13.64±0.35	0.89 (0.83–0.95)	0.001
Hospitalization days per patient-year	3.17±0.17	3.13±0.17	1.01 (0.87–1.18)	0.86
Patients with exacerbation — no. (%)‡				
Total	2001 (67.0)	2049 (68.2)	NA	0.35
Leading to hospitalization	759 (25.4)	811 (27.0)	NA	0.18

* Plus-minus values are means ±SE. NA denotes not applicable.

† The relative risks in this category were calculated with the use of Poisson regression corrected for treatment exposure and overdispersion.

‡ The comparisons in this category were calculated with the use of Fisher's exact test.

DISCUSSION

In our study, we showed that in the presence of freely prescribed respiratory medications (i.e., inhaled long-acting beta-agonists, inhaled corticosteroids, and theophyllines) other than another inhaled anticholinergic agent, tiotropium (at a dose of 18 µg once daily) did not alter the rate of decline in the mean FEV₁ in patients with COPD. However, lung function was significantly better than in the placebo group throughout the trial, and there were improvements in health-related quality of life and the rate of exacerbations.

As compared with results of previous long-term, prospective studies, the yearly rate of decline in FEV₁ that we observed was numerically lower than the rates of decline reported previously.^{2–6} Prospective interventional studies that were designed to examine the decline in FEV₁ — such as the European Respiratory Society Study on Chronic Obstructive Pulmonary Disease (EUROSCOP), the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) trial, the Lung Health Study II, and the Bronchitis Randomized on NAC [N-acetylcysteine] Cost–Utility Study (BRONCUS) — showed a decline in postbronchodilator rates ranging from 44 to 57 ml per year in the active-treatment groups and 47 to 69 ml per year in the placebo groups.^{3–6} In our study, the decline in lung function averaged 30 ml per year before bronchodilation and 41 ml per year after bronchodilation in the two study groups, a change that is less than that in any of the previous studies. The values for the decline in FEV₁

are also smaller than those observed in the post hoc analysis of lung function in the Towards a Revolution in COPD Health (TORCH) trial (ClinicalTrials.gov number, NCT00268216).²⁴

There are several potential explanations for the discrepancies in the rate of decline in our study, as compared with those in previous studies. First, our study design allowed for prescription of all respiratory therapies at the discretion of physicians, with the exception of another inhaled anticholinergic agent. It is therefore possible that the medical care that patients received during our study, including both short-acting and long-acting inhaled respiratory medications and aggressive treatment of exacerbations, differed from that in earlier trials and, as a whole, contributed to the generally lower rates of decline. However, such factors have not been definitively shown. Second, in our study, a higher proportion of patients with sustained abstinence from smoking tobacco may have resulted in a lower mean rate of decline. In our study, self-reports of smoking behavior indicated that only 30% of patients were current smokers at baseline, as compared with 38 to 90% in other studies.^{3–6} Third, other factors, such as differences in study design, selection of patients, and regional factors, could also account for discrepancies. In interpreting the results of our study, one should consider that the rates of decline in our study are similar to those reported for healthy nonsmokers and sustained quitters with mild-to-moderate COPD.²

Similar, low rates of decline in lung function were seen in the two study groups. A possible

Table 4. Incidence Rate of Serious Adverse Events per 100 Patient-Years.*

Adverse Event	Tiotropium (N = 2986)	Placebo (N = 3006)	Relative Risk for Tiotropium vs. Placebo (95% CI)
Cardiac	3.56	4.21	0.84 (0.73–0.98)†
Angina	0.51	0.36	1.44 (0.91–2.26)
Atrial fibrillation	0.74	0.77	0.95 (0.68–1.33)
Cardiac failure	0.61	0.48	1.25 (0.84–1.87)
Congestive heart failure	0.29	0.48	0.59 (0.37–0.96)†
Coronary artery disease	0.21	0.37	0.58 (0.33–1.01)
Myocardial infarction	0.69	0.97	0.71 (0.52–0.99)†
Lower respiratory	11.32	13.47	0.84 (0.77–0.92)†
Bronchitis	0.37	0.31	1.20 (0.73–1.98)
COPD exacerbation	8.19	9.70	0.84 (0.76–0.94)†
Dyspnea	0.38	0.62	0.61 (0.40–0.94)†
Pneumonia	3.28	3.46	0.95 (0.81–1.11)
Respiratory failure	0.90	1.31	0.69 (0.52–0.92)†

* Listed are the incidence rates of serious adverse events (excluding lung cancer) that were reported by more than 1% of patients in either study group, according to organ class during the study period (from the first day of administration of a study drug until the last day plus 30 days).

† $P < 0.05$.

explanation for this finding is that tiotropium does not influence the decline in lung function over time. There are other potential explanations. Current management of COPD could affect the decline in lung function so that a ceiling effect occurs and further improvements are not seen in the absence of an intervention that repairs or regenerates lung tissue. This possibility is supported by the high rate of prescriptions for concomitant respiratory medications in our study and by the differences between tiotropium and placebo in the rate of decline in postbronchodilator FEV₁ in patients who did not use inhaled corticosteroids or long-acting beta-agonists. Another potential reason is the higher rate of discontinuation in the placebo group. Data from our study and other trials suggest that patients who discontinue treatment have a more rapid decline in lung function than those who do not discontinue treatment.²⁵ Since patients who discontinued treatment had, on average, significantly more severe airflow obstruction at baseline, those in the placebo group who completed the trial probably represent “healthy survivors.” The possibility of a healthy-survivor effect may not be adequately addressed with the prespecified analysis presented here.^{25,26}

Tiotropium improved measures of airflow obstruction and vital capacity that were performed 24 hours after daily study-drug administration

during the 4-year study period. Tiotropium also improved lung function, as compared with placebo, beyond the improvement resulting from serial administration of maximal doses of salbutamol and ipratropium. These improvements in lung function were accompanied by improvements in some of the clinical outcomes measured. Scores regarding health-related quality of life improved relative to placebo during the entire 4-year study period. In the tiotropium group, there were significant delays in the onset of exacerbations and associated hospitalizations. These outcomes appeared in the presence of substantial use of concomitant COPD therapies.

The results of our study are consistent with the published pooled safety analysis²³ and indicate a reduction in cardiac adverse events associated with tiotropium. The reduced risk of respiratory failure was also observed in the previous pooled safety analysis of tiotropium, in which the relative risk of respiratory failure in the tiotropium group, as compared with the placebo group, was 0.59 (95% CI, 0.26 to 1.34).²³ However, our study had significantly more power to detect such differential event reporting because of a larger and longer exposure to tiotropium.

Our data show that among patients with COPD who were receiving other classes of respiratory medications during the study period, the addition of 18 μ g of tiotropium once daily for up

to 4 years did not result in changes in the rate of decline in lung function. However, there were important lung-function benefits associated with tiotropium that were maintained during the 4 years, as well as positive effects on health-related quality of life and a reduced risk of exacerbations and exacerbation-related hospitalizations consistent with a relevant effect on the clinical course of COPD. Finally, tiotropium reduced respiratory morbidity (including a decreased risk of respiratory failure) and reduced cardiac morbidity.

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REFERENCES

- Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Bethesda, MD: National Heart, Lung, and Blood Institute, April 2001 (revised 2007). (Accessed September 16, 2008, at <http://www.goldcopd.org>.)
- Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV₁: the Lung Health Study. *JAMA* 1994; 272:1497-505.
- The Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med* 2000;343:1902-9.
- Pauwels RA, Löfdahl CG, Laitinen LA, et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. *N Engl J Med* 1999;340: 1948-53.
- Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000;320:1297-303.
- Decramer M, Rutten-van Mölken M, Dekhuijzen PN, et al. Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. *Lancet* 2005;365:1552-60. [Erratum, *Lancet* 2005;366:984.]
- Soriano JB, Sin DD, Zhang X, et al. A pooled analysis of FEV₁ decline in COPD patients randomized to inhaled corticosteroids or placebo. *Chest* 2007;131:682-9.
- Casaburi R, Mahler DA, Jones PW, et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002;19: 217-24.
- O'Donnell DE, Flüge T, Gerken F, et al. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J* 2004;23:832-40.
- Maltais F, Hamilton A, Marciniuk D, et al. Improvements in symptom-limited exercise performance over 8 h with once-daily tiotropium in patients with COPD. *Chest* 2005;128:1168-78.
- Vincken W, van Noord JA, Greefhorst APM, et al. Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. *Eur Respir J* 2002; 19:209-16.
- Brusasco V, Hodder R, Miravittles M, Korducki L, Towse L, Kesten S. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. *Thorax* 2003;58:399-404. [Erratum, *Thorax* 2005;60:105.]
- Niewoehner DE, Rice K, Cote C, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator. *Ann Intern Med* 2005;143: 317-26.
- Anzueto A, Tashkin D, Menjoge S, Kesten S. One-year analysis of longitudinal changes in spirometry in patients with COPD receiving tiotropium. *Pulm Pharmacol Ther* 2005;18:75-81.
- Decramer M, Celli B, Tashkin DP, et al. Clinical trial design considerations in assessing long-term functional impacts of tiotropium in COPD: the UPLIFT trial. *COPD* 2004;1:303-12.
- Quanjer PH. Standardised lung function testing: report of the European Com-
- community for Coal and Steel. *Bull Eur Physiopathol Respir* 1983;19:Suppl:7-28.
- American Thoracic Society. Standardization of spirometry: 1994 update. *Am J Respir Crit Care Med* 1995;152:1107-36.
- Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation: the St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992;145: 1321-7.
- Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics* 1982;38:963-74.
- Suissa S. Statistical treatment of exacerbations in therapeutic trials of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006;173:842-6.
- Tashkin DP, Celli B, Decramer M, et al. Bronchodilator responsiveness in patients with COPD. *Eur Respir J* 2008;31:742-50.
- Spiriva HandiHaler. Ingelheim, Germany: Boehringer Ingelheim Pharma GmbH, 2008 (package insert).
- Kesten S, Jara M, Wentworth C, Lanes S. Pooled clinical trial analysis of the safety of tiotropium. *Chest* 2006;130: 1695-703.
- Celli BR, Thomas NE, Anderson JA, et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. *Am J Respir Crit Care Med* 2008;178:332-8.
- Calverley PM, Spencer S, Willits L, Burge PS, Jones PW. Withdrawal from treatment as an outcome in the ISOLDE study of COPD. *Chest* 2003;124:1350-6.
- Kesten S, Plautz M, Piquette CA, Habib MP, Niewoehner DE. Premature discontinuation of patients: a potential bias in COPD clinical trials. *Eur Respir J* 2007;30: 898-906.

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