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Mortality in the 4-Year Trial of Tiotropium (UPLIFT) in Patients with Chronic Obstructive Pulmonary Disease

Bartolome Celli¹, Marc Decramer², Steven Kesten³, Dacheng Liu³, Sunil Mehra⁴, and Donald P. Tashkin⁵, on behalf of the UPLIFT Study Investigators*

¹Brigham and Women's Hospital and St. Elizabeth's Medical Center, Boston, Massachusetts; ²University of Leuven, Leuven, Belgium; ³Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut; ⁴Pfizer Pharmaceuticals, New York, New York; and ⁵David Geffen School of Medicine at UCLA, Los Angeles, California

Rationale: In the 4-year UPLIFT trial, tiotropium improved lung function and health-related quality of life and decreased exacerbations compared with usual respiratory medications except inhaled anticholinergics in patients with chronic obstructive pulmonary disease (COPD). Mortality and its causes was a secondary endpoint in UPLIFT.

Objectives: We describe the effect of tiotropium on survival and analyze differences between mortality during treatment and during follow-up of discontinued patients.

Methods: This study involved a randomized, double-blind trial comparing tiotropium with placebo in patients with COPD (≥ 40 yr of age; postbronchodilator FEV₁ $\leq 70\%$; FEV₁/FVC $\leq 70\%$). Mortality was evaluated during treatment and with follow-up of discontinued patients. Cause of death was adjudicated by an endpoint committee. **Measurements and Main Results:** A total of 5,993 patients were randomized, 3,006 to placebo and 2,987 to tiotropium. While patients were receiving treatment, there were 792 deaths, with a lower risk in the tiotropium group (hazard ratio, 0.84; 95% confidence interval [CI], 0.73–0.97). Statistical significance was observed at the end of the protocol-defined treatment period ($P = 0.034$) but not 30 days thereafter ($P = 0.086$). Adjustment by GOLD stage, sex, age, baseline smoking behavior, and baseline respiratory medications subgroups did not alter the results of the analysis. The most common causes of death adjudicated by an independent endpoint committee were lower respiratory, cancer, general disorders, and cardiac disorders. The hazard ratios for lower respiratory and cardiac mortality during treatment were 0.86 (95% CI, 0.68–1.09) and 0.86 (95% CI, 0.75–0.99), respectively.

Conclusions: Treatment with tiotropium over 4 years is associated with decreased mortality, with the effect being most prominent in the cardiac and respiratory systems.

Keywords: COPD; tiotropium; mortality

Chronic obstructive pulmonary disease (COPD) is an important cause of morbidity and mortality (1). Several interventions have been shown to decrease mortality in COPD, including smoking cessation (2), noninvasive ventilation for respiratory failure (3), supplemental oxygen in those who have persistent hypoxemia (4, 5), and lung-volume reduction surgery in selected patients (6). In the recently completed TORCH trial, treatment with salmeterol plus fluticasone over 3 years showed a decrease in mortality that almost reached statistical significance and raised the possibility that pharmacotherapy could affect survival (7).

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* A complete list of the UPLIFT Study Investigators can be found in the online supplement to this article.

Correspondence and requests for reprints should be addressed to Bartolome Celli, M.D., Pulmonary and Critical Care Division, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115. E-mail: bcelli@copdnet.org

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

There is limited knowledge on the effect of pharmacotherapy on mortality in patients with chronic obstructive pulmonary disease, although the results of the TORCH study support a benefit in patients receiving the combination of inhaled fluticasone and salmeterol.

What This Study Adds to the Field

This study shows that pharmacotherapy with tiotropium reduces mortality compared with usual care while patients are receiving treatment. These results provide support that disease progression can be affected by pharmacotherapy.

Tiotropium is a once-daily, inhaled anticholinergic that provides at least 24 hours of improvement in airflow and hyperinflation in patients with COPD (8–11). The results of the UPLIFT (Understanding Potential Long-Term Impacts on Function with Tiotropium) trial, which tested whether tiotropium could reduce the rate of decline in FEV₁ in patients with COPD who were permitted treatment including use of short- and long-acting respiratory medications other than inhaled anticholinergics, have been recently published (12). Although there was no difference in the rate of FEV₁ decline over placebo, at all time points patients receiving tiotropium had significant improvements in lung function and health-related quality of life (HRQoL) and had a reduced risk for exacerbations, episodes of respiratory failure, and hospitalizations due to COPD exacerbations compared with patients receiving placebo. In addition, a reduced risk for all-cause mortality was reported. This study presents a more in-depth analysis of the effect of tiotropium and its discontinuation on mortality and its causes, which was a prespecified secondary end-point in UPLIFT. Partial results from this analysis have been presented at a national meeting (13).

METHODS

Details of the study design and results on the primary and secondary endpoints have been previously reported (12, 14). All patients gave written informed consent, and the study was approved by local ethical review boards and conducted in accordance with the Declaration of Helsinki.

Study Design

The study was a 4-year, randomized, double-blind, placebo-controlled, parallel-group trial in patients with COPD in which all patients were permitted to continue use of all respiratory medications other than inhaled anticholinergics. The primary endpoints were yearly rate of decline of pre- and postbronchodilator lung function until completion

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of the double-blind treatment. Secondary outcome included other lung function measures, HRQoL as measured by the St. George's Respiratory Questionnaire (SGRQ) total score, COPD exacerbations and related hospitalizations, and mortality.

Patients were recruited from 490 investigational centers in 37 countries. Criteria for participation included diagnosis of COPD, age at least 40 years, smoking history of at least 10 pack-years, and postbronchodilator FEV₁ ≤70% of the predicted normal and FEV₁ ≤70% of FVC. Postrandomization clinic visits occurred at 1 month, at 3 months, and then every 3 months throughout the 4-year treatment period.

The treatment arms were tiotropium 18 µg once daily or matching placebo delivered via the HandiHaler inhalation device (Boehringer Ingelheim GmbH and Co. KG, Ingelheim, Germany). All respiratory medications, other than inhaled anticholinergics, were permitted during the trial. At study drug termination (approximately Day 1,440), all patients were asked to stop the trial drug and instructed to take ipratropium two actuations (40 µg) four times daily and to return for a final assessment after a 30-day study drug termination (approximately Day 1,470) defined as the "washout period."

Mortality

Mortality was collected on standard adverse event case report forms as well as through a trial-specific vital status case report form for patients who prematurely discontinued study drug. The vital status case report form referenced whether the patient was known to be alive as of a specific date recorded on the top of the page. For patients who completed all study visits, vital status information was considered complete at the time of exiting the study. The last treatment visit was not necessarily scheduled precisely at Day 1,440 (protocol-defined end-of-treatment period) and may have occurred at an earlier or later date due to standard expected issues on scheduling visits over 4 years. The same is true for the follow-up visit (30 days after the last treatment visit). The last study visit (at the end of the "washout period") varied from approximately 45 to 49 months (corresponding to approximately Day 1,350 to Day 1,492). No additional efforts for collection of survival information were made beyond the last study visit because the patient was considered to have completed the full protocol; however, survival information beyond this point became known for some of these patients through a variety of sources.

Adverse events, including those deemed serious and fatal, were coded using the Medical Dictionary for Regulatory Activities, version 11.0. The name assigned to the event is referred to as a preferred term. Each preferred term is encompassed under a predefined system organ class. For the purpose of maintaining consistency across the tiotropium projects, the Medical Dictionary for Regulatory Activities system organ classes were, *a priori*, slightly modified. Certain preferred terms are clinically similar and were *a priori* combined to improve the precision of the estimate of rates.

A mortality adjudication committee consisting of three independent physicians (two pulmonologists and one cardiologist) who were not UPLIFT investigators determined a primary cause of death from available information. For the purposes of this study, only the adjudicated cause of death is being reported; however, selected differences from the investigator judgment are noted in the RESULTS section.

Other Procedures

Spirometry was performed according to American Thoracic Society guidelines (15) at randomization, at 30 days and every 6 months throughout the treatment period, and at a follow-up visit approximately 30 days after the end of study treatment. Study drug was administered immediately after prebronchodilator spirometry and just before short-acting bronchodilator administration. All 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 (14). HRQoL was measured using the SGRQ before prebronchodilator spirometry testing at baseline and every 6 months (16).

Exacerbations were defined as an increase in or new onset of more than one respiratory symptom (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three or more days requiring treatment with an antibiotic and/or systemic steroid. Data from COPD

exacerbations and related hospitalizations were collected on study-specific case report forms at every visit.

Data were reviewed throughout the trial by an independent Data and Safety Monitoring Board. The last clinic visits of the 34 patients remaining in the trial after January 31, 2008 were accelerated as recommended by the DSMB after their review of the data in October 2007, in which they observed a lower mortality rate in the tiotropium group. The reason for the recommendation was not communicated to the trial team until after unblinding.

Data Analysis

All patients who were randomized and received study medication were included in the analysis of mortality following the intent-to-treat principle. Survival functions for tiotropium and placebo were derived from the Kaplan-Meier estimates and compared using the log-rank test. Cox's proportional hazards model was used to estimate the hazard ratio between the two treatment arms with time to death as the outcome variable and treatment as explanatory variable. Subgroup analyses were performed for smoking status, age, sex, GOLD stage, body mass index (BMI), and baseline pulmonary medication use. Event incidence rate was calculated for each treatment group as the number of patients with events divided by the time at risk and expressed per 100 patient-years.

Mortality was analyzed under three conditions: deaths occurring on-treatment (i.e., until 30 d after the last dose of study drug treatment) (condition A), deaths occurring in all patients until the end of the protocol-defined treatment period (Day 1,440) (condition B), and deaths occurring in all prematurely discontinued patients until the end of the 30-day washout (Day 1,470) (condition C). A fatal event was considered "on-treatment" if the onset of the event occurred within 30 days of the last dose of medication. For conditions B and C, the analysis is based on the date of death occurring before the specified date (i.e., on Day 1,440 or 1,470). For the cumulative HR estimates, day-specific HRs and CIs were obtained by artificially censoring known follow-up times at the given day. A separate proportional hazards model was then fit at each day to the data obtained by censoring future information at that time point. The follow-up times included information from on-treatment and prematurely discontinued sources.

Data are reported as means ± SD unless otherwise specified. Statistical significance was considered at $P < 0.05$.

RESULTS

Study Population

There were 5,993 randomized patients (3,006 to placebo and 2,987 to tiotropium). The baseline demographics have been previously reported. The mean age was 65 ± 8 years, 75% of the patients were men, and 30% were smoking at randomization. Mean prebronchodilator FEV₁ was 1.10 ± 0.40 L (39% predicted) and postbronchodilator FEV₁ was 1.32 ± 0.44 L (48% predicted). Approximately 44.6% of the control population prematurely discontinued study drug, compared with 36.2% of patients treated with tiotropium. Compared with those who completed study drug per protocol, patients who prematurely discontinued study drug had a lower baseline prebronchodilator FEV₁ (37% predicted vs. 41% predicted; $P < 0.001$). Baseline medication use was highly prevalent: approximately 62% of patients used an inhaled steroid, 60% used a long-acting β-agonist, and 23% used theophylline-containing preparations. Inhaled anticholinergics, used by 45% of patients, were stopped at randomization.

Mortality

The hazard ratio (HR) for all-cause mortality was previously reported and is summarized in Table 1. The total number of reported deaths from any cause during study drug treatment (i.e., on-treatment) was 411 (13.6%) in the placebo group and 381 (12.8%) in the tiotropium group (HR [tiotropium/placebo], 0.84; 95% confidence interval [CI], 0.73–0.97; $P = 0.016$). For the full 4-year, protocol-defined treatment period (1,440 days),

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TABLE 1. MORTALITY RATES AND HAZARD RATIOS DURING THE TREATMENT PERIOD AND INCLUDING THE VITAL STATUS INFORMATION FROM PATIENTS PREMATURELY DISCONTINUING STUDY DRUG

	Control		Tiotropium		Tiotropium vs. Control	
	N (%)	N (%)	ΔRates (%)	HR (95% CI)	P Value	
On-treatment	411 (13.7)	381 (12.8)	0.9	0.84 (0.73–0.97)	0.016	
Day 1,440	491 (16.3)	430 (14.4)	1.9	0.87 (0.76–0.99)	0.034	
Day 1,470	495 (16.5)	446 (14.9)	1.6	0.89 (0.79–1.02)	0.086	
All	514 (17.1)	467 (15.6)	1.5	0.89 (0.78–1.00)	0.058	

Definition of abbreviation: HR = hazard ratio.

there were 921 deaths. Mortality was significantly lower in patients randomized to tiotropium compared with placebo (HR, 0.87; 95% CI, 0.76–0.99; $P = 0.034$). For the period of 4 years + 30 days (1,470 days), there were 941 deaths, with a lower risk of death in the tiotropium group, although the upper limits of the CI crossed 1 (HR, 0.89; 95% CI, 0.79–1.02; $P = 0.086$). Between Days 1,440 and 1,470, there were four deaths in the placebo group and 16 deaths in the tiotropium group. The four deaths in the placebo group occurred over 200 days after termination of study drug, and none had completed the study according to protocol. However, 6 of 16 deaths in the tiotropium group had completed the full study treatment period (i.e., completed the trial according to protocol) and had died between 9 and 33 days after termination of tiotropium. For 3 out of 10 additional patients in the tiotropium group who died between Days 1,440 and 1,470 but had discontinued the study drug prematurely, death occurred less than 35 days after tiotropium was discontinued.

The accounting of the vital status information available for patients (discontinued and completed) until Day 1,440 and until Day 1,470 is displayed in Table 2. Approximately 5% of patient data is missing at Day 1,440 compared with 25% at Day 1,470. We have examined the database for the number of days patients were receiving study drug during the trial and note that 39% of

TABLE 2. ACCOUNTING OF AVAILABLE VITAL STATUS DATA AT DAYS 1,440 AND 1,470 BY TREATMENT GROUP

	Placebo	Tiotropium	Total
	N (%)	N (%)	N (%)
Total	3,006 (100)	2,986 (100)	5,992 (100)
Day 1,440			
Unknown	164 (5.5)	137 (4.6)	301 (5.0)
Known	2,842 (94.5)	2,849 (95.4)	5,691 (95.0)
Alive	2,351 (78.2)	2,419 (81.0)	4,770 (79.6)
Dead	491 (16.3)	430 (14.4)	921 (15.4)
Day 1,470			
Unknown	741 (24.7)	736 (24.7)	1,477 (24.7)
Known	2,265 (75.4)	2,250 (75.7)	4,515 (75.4)
Alive	1,770 (58.9)	1,804 (60.4)	3,574 (59.6)
Dead	495 (16.5)	446 (14.9)	941 (15.7)

patients were still recorded as receiving study drug as of Day 1,440, but only 2.2% were receiving study drug as of Day 1,470.

Vital status information was occasionally received beyond Day 1,470. Including all known data, there were 981 deaths with a lower risk for the tiotropium group (HR, 0.89; 95% CI, 0.78–1.00; $P = 0.058$) (Table 1). Figure 1 displays the HRs and 95% CIs from Day 1,340 until Day 1,510.

The demographics of patients who died during the treatment period and after premature discontinuation of study drug until Day 1,440 are documented in Table 3. Patients who died had more severe disease at baseline, were older, had lower BMI, and were more often male, compared with those who did not die before Day 1,440.

Subgroups

The effects of tiotropium on mortality were analyzed across sex; age groups; baseline smoking behavior; GOLD stage and baseline LABA, ICS, LABA+ICS; and inhaled anticholinergic use (Figures 2–4). The results were consistent across these subgroups; treatment-by-subgroup interactions were not signif-

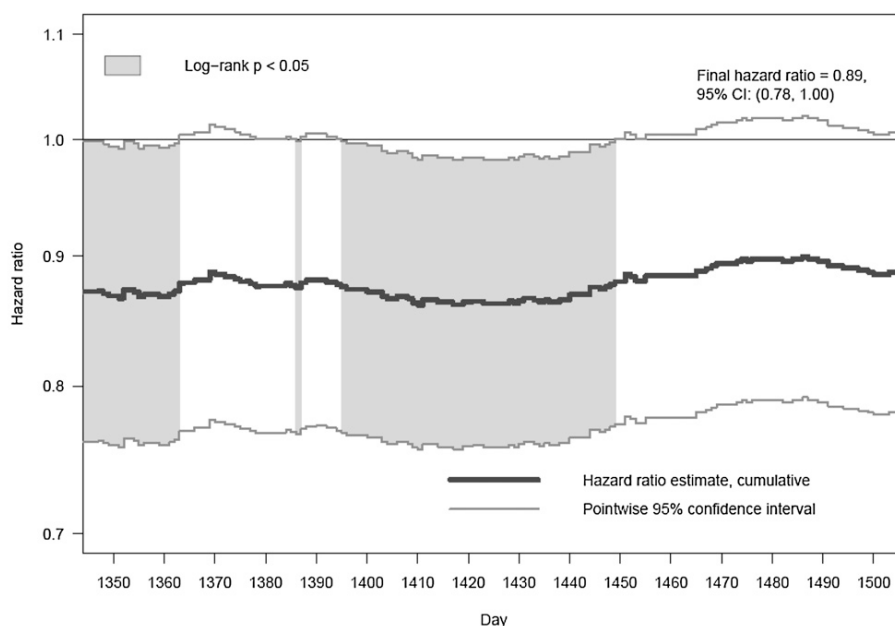


Figure 1. Hazard ratios (tiotropium/control) and 95% confidence intervals for mortality including data from prematurely discontinued patients from Day 1,340 to Day 1,510. Cumulative censoring represents the total number of censored patients up to each time point.

mulative censoring:

Tiotropium	59	61	61	62	62	73	86	97	112	137	178	225	736	2006	2187	2322
Control	83	84	84	84	88	95	117	129	145	164	196	249	741	2024	2187	2289

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TABLE 3. BASELINE DEMOGRAPHICS OF PATIENTS BY TREATMENT AND VITAL STATUS (ON-TREATMENT, AT DAY 1,440, AND AT DAY 1,470)

	Survived		Died	
	Placebo	Tiotropium	Placebo	Tiotropium
On-treatment				
N	2,595	2,605	411	381
Age	64 (8)*	64 (8)	68 (8)	68 (8)
Sex (% female/male)	27/73	25/75	19/81	19/81
Smoker (% current/ex)	30/70	29/71	27/73	33/67
BMI	26 (5)	26 (5)	25 (5)	25 (6)
Post-BD FEV ₁ (L)	1.34 (0.4)	1.35 (0.4)	1.16 (0.4)	1.16 (0.4)
Post-BD FEV ₁ (% pred)	48 (12)	49 (13)	43 (13)	43 (13)
Day 1,440				
N	2,515	2,556	491	430
Age	64 (8)	64 (8)	68 (8)	68 (8)
Sex (% female/male)	27/73	25/75	19/81	20/80
Smoker (% current/ex)	30/70	29/71	27/73	32/68
BMI	26 (5)	26 (5)	25 (5)	25 (6)
Post-BD FEV ₁ (L)	1.35 (0.4)	1.36 (0.4)	1.14 (0.4)	1.14 (0.4)
Post-BD FEV ₁ (% pred)	48 (12)	48.6 (13)	42 (13)	42 (13)
Day 1,470				
N	2,511	2,540	495	446
Age	64 (8)	64 (8)	68 (8)	68 (8)
Sex (% female/male)	27/73	25/75	19/81	19/81
Smoker (% current/ex)	30/70	29/71	28/72	32/68
BMI	26 (5)	26 (5.0)	25 (5)	25 (6)
Post-BD FEV ₁ (L)	1.35 (0.4)	1.36 (0.4)	1.14 (0.4)	1.14 (0.4)
Post-BD FEV ₁ (% pred)	48 (12)	48 (12)	42 (13)	42 (13)

Definition of abbreviations: BD = bronchodilator; BMI = body mass index.

* Numbers in parentheses are SD.

icant except for the BMI and smoking subgroups for all-cause mortality (all deaths including vital status with censoring at 1,470 days). For example, the HR for tiotropium to placebo for all-cause mortality was 0.82 (95% CI, 0.71–0.96) for exsmokers and 1.09 (95% CI, 0.86–1.38) for current smokers (all deaths including vital status with censoring at Day 1,470). In general, the lack of interaction is consistent, and the results suggest no major effect in any specific subpopulation of patients, although

the HRs based on smoking behavior at baseline suggests that continued smoking may have a negative impact on the mortality benefits observed with tiotropium.

Most Common Causes of Death

Organ class. Only organ classes where the frequency of death occurred in at least 1% of the study cohort are shown in Table 4. The most common cause of death was lower respiratory disorders. The next two most common classes were other respiratory disorders (predominantly lung cancer) and general disorders. The preferred terms death (constituting death of unknown cause), sudden death, and sudden cardiac death are, by nomenclature, classified under general disorders.

Preferred terms. Preferred terms are displayed where the frequency of death occurred in at least 0.1% of the study cohort (see Table 1). The most common terms were respiratory, neoplastic or cardiovascular, COPD exacerbations, and lung cancer; lung cancer was the most common overall. There was no pattern suggesting a significant increase in risk on a preferred term level, and none of the individual terms for fatal events showed a significantly decreased risk.

Certain differences between investigator-reported and adjudication committee-reported diagnosis should be recognized. The adjudication committee only recorded myocardial infarction where documented objective evidence was provided in the available record. This decreased the number of cardiac events noted by the investigator. For example, in the on-treatment analysis, there were 36 investigator-reported myocardial infarction events, compared with 17 after adjudications by the committee. The HR (tiotropium/placebo) from the investigator-judged reporting for myocardial infarction was 0.59 (95% CI, 0.30–1.15). The rate ratio for pneumonia was greater than 1 according to the adjudicated event with wide confidence intervals, but it was 0.95 (95% CI, 0.58–1.56) based on investigator reporting. There were more fatal cases reported under general disorders, particularly the terms death and sudden cardiac death, in the adjudication process compared with the investigator judgment. However, the rate ratio for general disorders remained less than 1 with the CI including the value

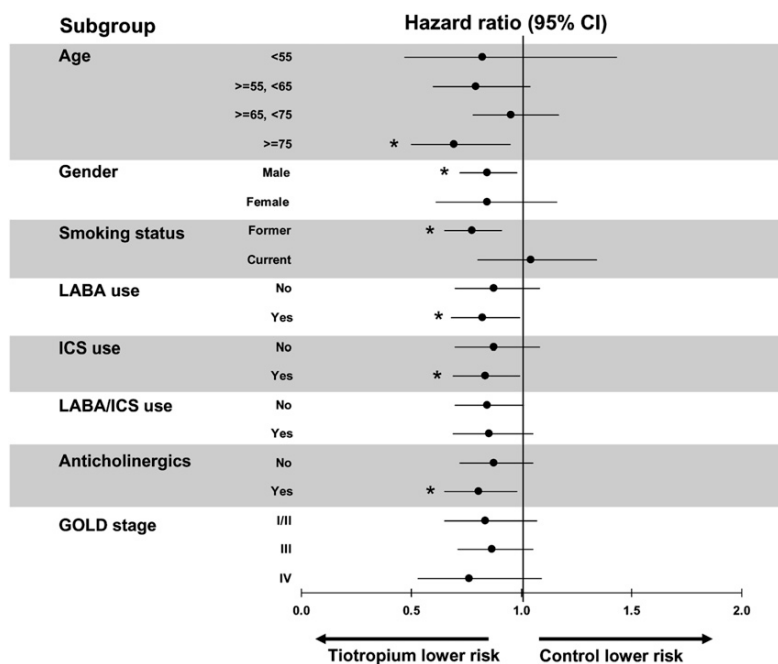


Figure 2. Hazard ratios (tiotropium/control) and 95% confidence intervals for mortality during study drug treatment (on-treatment) according to major subgroups of interest; $P < 0.05$ tiotropium versus control.

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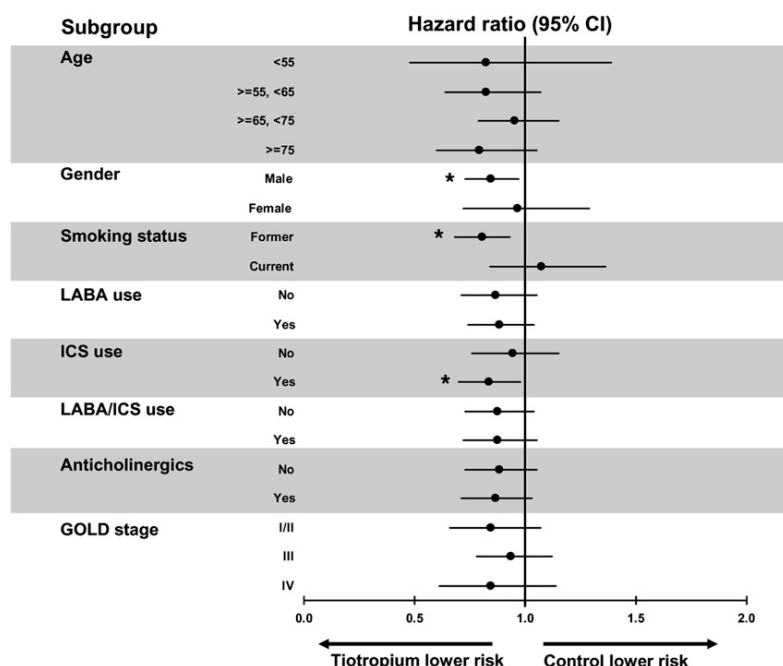


Figure 3. Hazard ratios (tiotropium/control) and 95% confidence intervals for mortality during study drug treatment and including data from vital status of discontinued patients for the protocol-defined treatment period (until Day 1,440) according to major subgroups of interest; $P < 0.05$ tiotropium versus control.

of 1. There was no evidence of an excess risk for fatal stroke with the HR being less than 1 for the on-treatment analysis and for the analysis including vital status, albeit with an upper limit of the CI including 1 due to the relatively small number of cases.

DISCUSSION

The UPLIFT trial was designed to assess the effect of tiotropium on the clinical course of patients with COPD who were permitted to use all respiratory medications (other than inhaled

anticholinergics) throughout the trial. In UPLIFT, patients receiving tiotropium had improved survival during the 4-year treatment period compared with patients in the control group. The findings were consistent across major subgroups of interest. In the 30 days after the 4-year treatment period, the magnitude of the effect decreased such that nominal statistical significance was no longer present. These results provide further support to the observation that COPD mortality can be positively influenced with tiotropium (12).

The beneficial effect of tiotropium on mortality is supported by improvement in the other clinically important endpoints

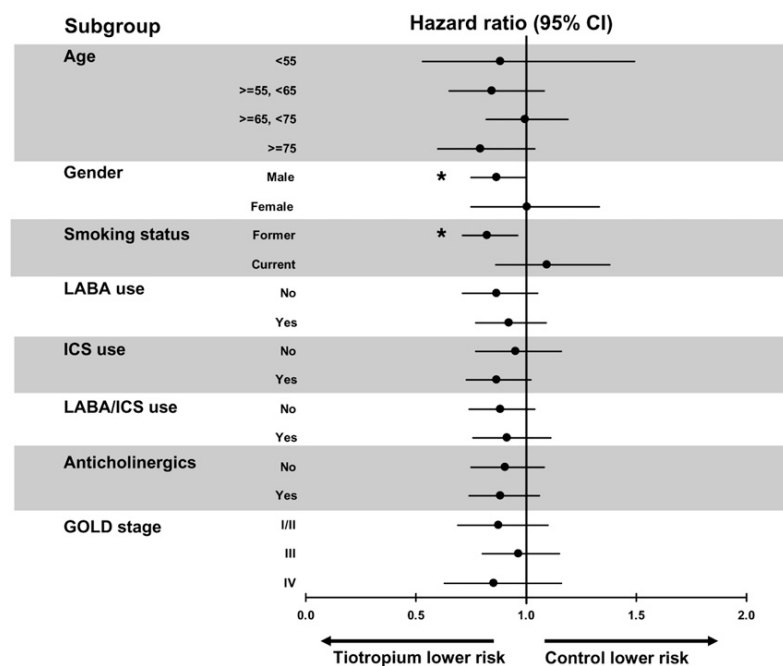


Figure 4. Hazard ratios (tiotropium/control) and 95% confidence intervals for mortality during study drug treatment and including data from vital status of discontinued patients to the end of the 30-day washout period (until Day 1,470) according to major subgroups of interest; $P < 0.05$ tiotropium versus control.

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TABLE 4. MOST COMMON CAUSES OF DEATH ($\geq 0.5\%$ OF POPULATION) ACCORDING TO SYSTEM ORGAN CLASS AS DETERMINED BY THE ADJUDICATION COMMITTEE DURING TREATMENT, INCLUDING VITAL STATUS INFORMATION UNTIL DAY 1,440 AND VITAL STATUS INFORMATION UNTIL DAY 1,470

System Organ Class	Incidence Rate (per 100 patient-years)		Rate ratio (95% CI), Tiotropium vs. Control
	Control (n = 3,006)	Tiotropium (n = 2,986)	
On-treatment			
Respiratory system disorders (lower)	1.62	1.39	0.86 (0.68–1.09)
Respiratory system (other)	0.84	0.88	1.05 (0.77–1.44)
General	0.82	0.61	0.75 (0.53–1.07)
Neoplasms	0.50	0.39	0.78 (0.50–1.20)
Cardiac	0.30	0.25	0.86 (0.75–0.99)
Nervous system	0.19	0.16	0.81 (0.41–1.63)
Day 1,440			
Respiratory system disorders (lower)	1.59	1.36	0.85 (0.69–1.06)
General	0.94	0.81	0.85 (0.64–1.14)
Respiratory system (other)	0.73	0.80	1.10 (0.81–1.49)
Neoplasms	0.42	0.32	0.76 (0.49–1.18)
Cardiac	0.29	0.23	0.80 (0.47–1.36)
Nervous system	0.19	0.14	0.71 (0.37–1.38)
Day 1,470			
Respiratory system disorders (lower)	1.58	1.39	0.88 (0.71–1.09)
General	0.93	0.80	0.86 (0.65–1.15)
Respiratory system (other)	0.73	0.81	1.11 (0.82–1.50)
Neoplasms	0.42	0.34	0.82 (0.54–1.26)
Cardiac	0.29	0.23	0.81 (0.48–1.01)
Nervous system	0.19	0.14	0.76 (0.40–1.45)

Definition of abbreviation: CI = confidence interval.

evaluated in the UPLIFT study. Sustained improvement in lung function with tiotropium relative to the control group was accompanied by improvement in HRQoL over the 4-year study period. Indeed, at study end, the HRQoL score in the tiotropium group had not returned to the baseline value. There were also significant delays in the onset of an exacerbation and associated hospitalization, as well as reductions in the number of exacerbations, although not in the number of hospitalizations. Poor HRQoL score and severe exacerbations including hospitalizations represent risk factors for subsequent mortality in patients with COPD (17–19).

The selection of the method for the optimal analysis of mortality in drug trials deserves discussion because the method of analysis affects the results and influences the final interpretation. We have not favored any analysis in this report and strongly believe that all data must be considered to arrive at the most appropriate conclusion. The most popular method follows the intention-to-treat (ITT) approach. In this approach, the analysis is based on the initial treatment intent and not necessarily on the treatment administered. The patients are followed throughout the intended period of observation after randomization, whether or not patients withdrew from the trial. The analysis is conducted as if the patient had received the allocated therapy, even if they did not receive the therapy if they had prematurely discontinued study drug (20). Events are usually censored after the intended period to avoid tail instability of the estimated survival curve. There are two options for the determination of this cut-off date: (1) Use the last intended day of medication and (2) include a follow-up period that captures any residual medication effects. Different information is provided depending on the selection of the date. ITT gives a pragmatic estimate of the utility of a treatment for clinical practice when used in individuals but has limitations when testing if the outcome is attributed to the pharmacological action of the study drug (20). The two major attribution limitations of the aforementioned ITT approach are (1) attribution to a distant event and (2) attribution when the control

group is receiving the active drug under study after study drug discontinuation. For example, in UPLIFT, under the first situation, patient A receives placebo, discontinues the study drug after a short period (i.e., 1 month) due to an exacerbation, and dies 3 years later. The death would be attributed to placebo despite the patient having not received the placebo for 3 years. Consider the second situation in which the same patient is prescribed marketed tiotropium upon discontinuation of study drug and dies 3 years later. The death would be attributed to placebo despite the patient having received 3 years of continuous treatment with tiotropium. The UPLIFT data suggest a survival benefit with tiotropium; however, any benefit versus control would narrow as more control patients receive tiotropium. Given the widespread use of tiotropium, such an attenuation of any benefit would tend to increase with the duration of the trial and follow-up of discontinued patients.

A strong argument can be stated for consideration of another method of analysis of survival considering only the time that patients receive the study drug. An additional period of attribution can be attached that considers residual effects of medication. In UPLIFT, we have referred to this as the “on-treatment” analysis. The event is considered on-treatment if the onset occurred within 30 days of the last dose of study drug. Mechanistically, the assumption is that sustained 24 hours of airway patency is the major attribute of tiotropium that leads to a survival benefit. Such a mechanism could potentially result in decreased exacerbations with its beneficial consequences. Other mechanisms, such as antiproliferative and antiinflammatory effects, have been observed under laboratory conditions and should be considered speculative and hypothesis-generating at this time (21–23). Therefore, there should be no survival benefit in those not receiving tiotropium, and it is unlikely that the survival benefits would persist in the absence of drug. The on-treatment analysis provides the most direct assessment of the pharmacological action and benefits of receiving tiotropium but not necessarily the act of prescribing the drug (which may be confounded by issues of adherence and persistence). Further-

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more, the on-treatment analysis inherently is biased against showing a benefit of tiotropium on survival. Survival is related to the severity of the underlying respiratory disease (24, 25). In UPLIFT, as in other trials, patients who are more severe (i.e., at highest risk of death) prematurely discontinue study medication at a much higher rate than patients who have better respiratory health (26). Because premature discontinuation preferentially occurs in the control group not receiving tiotropium, the on-treatment analysis would trend toward diminishing the survival benefits of the active drug.

In UPLIFT, there was a difference in the significance of the mortality results at 1,440 days versus 1,470 days. The possible explanations deserve discussion. First, the investigators were provided with a vital status case report form to complete that referenced whether the patient was known to be alive as of a specific date on the page. The intention of the procedure was to obtain information on vital status up to 4 years from randomization; however, due to discrepancies in the implementation of the procedure in different countries, the dates recorded on the case report form varied, which explains the diminishing amount of full information out to Day 1,470 (i.e., including the protocol-defined washout period). Second, the DSMB recommended an acceleration of the last clinic visit of the 34 patients remaining in the trial after January 31, 2008 due to a benefit in decreased mortality in the tiotropium arm (the reason was provided only after unblinding). This resulted in a shortened follow-up period for these remaining patients. In spite of that, the collection procedure resulted in complete vital status data being available in 95% of patients for the protocol-defined treatment period of 1,440 days. The HR for mortality was 0.87 (95% CI, 0.76–0.99), where the upper boundary of the CI is less than 1. On the other hand, the data including a further 30 days beyond 4 years (reflecting the follow-up period during which tiotropium patients would be discontinued from tiotropium and all patients were to receive ipratropium) showed a HR of 0.89 (95% CI, 0.79–1.02), with the upper boundary crossing 1. In addition, there were deaths reported beyond 1,470 days (i.e., >4 yr + 30 d). The HR for death including all available data collected is 0.89 (95% CI, 0.78–1.00), thus highlighting the sensitivity of the CIs as time is extended beyond the 4-year treatment period. A third possible reason for the difference of mortality at 1,440 versus 1,470 days may relate to the effect of withdrawing treatment in the active arm. Six of the 16 patients treated with tiotropium who died during this interval did so after completing the per protocol treatment period as planned, whereas all of the deaths in the placebo group occurred more than 200 days after discontinuation of treatment before Day 1470, consistent with a bias in discontinuation rates. It is possible that discontinuation of tiotropium resulted in the cessation of its beneficial effect and an upward adjustment of the death rate that subsequently approached that of the control group.

The mortality hazard rates with CIs between Days 1,350 and 1,490 (Figure 1) show consistent results. It can be seen that the risk ratio oscillates over a relatively narrow band, showing a persistent benefit of tiotropium with HRs less than 0.9 throughout that time frame. The concomitant upper CI value crosses the 1 value around that oscillatory pattern after the 1,440 days but remains very close to nominal statistical significance.

Subgroup analyses were performed to examine whether a specific subgroup may have been responsible for skewing the results in favor of tiotropium. The subgroups were based on baseline characteristics of the patients and show a general consistency, although slight differences can be observed based on male sex and baseline self-reported smoking behavior. The beneficial effect of tiotropium on mortality in nonsmokers was

not apparent in patients who were continued smokers at baseline, suggesting that the noxious effect of smoking may override the benefits of therapy; however, smoking behavior during therapy may also influence the findings and can be confounded by study medication assignment.

There are recent data to consider when viewing the mortality results from UPLIFT. The overall mortality percentage in UPLIFT at 4 years was higher than that observed in TORCH at 3 years, but the annualized rate was lower (7). In both trials, the treatment arms showed improved survival compared with control subjects, supporting the concept that pharmacotherapy has a beneficial effect on survival in COPD. In TORCH, there was a 2-week follow-up period for which the mortality data were not analyzed. Such analysis would have provided important information regarding the effect of discontinuation of treatment in that population. In a 2-year study of patients with severe and very severe COPD with a history of exacerbations, tiotropium was equally effective on exacerbations with a lower rate of pneumonia but had a higher number of fatal events compared with the combination of salmeterol and fluticasone (27). In that trial, mortality was a tertiary end-point, and the results were confounded by the run-in with 2 weeks of prednisolone and salmeterol being suddenly withdrawn at randomization (destabilization of patients), failure to follow patients who discontinued prematurely, and the biases introduced by withdrawal of inhaled steroids used by 51% of patients at baseline (27–29). Recent data from a longitudinal population-based cohort study reported a reduced risk of mortality with tiotropium relative to salmeterol (HR, 0.80; 95% CI, 0.70–0.93) in patients with COPD during the 6 months after discharge from hospital due to COPD; these findings support the beneficial effect on mortality observed in UPLIFT (30). In addition, a previous publication of tiotropium clinical trial data indicated reported trends toward reduced all-cause, lower respiratory and cardiovascular mortality (31, 32).

In summary, in the setting of allowing all other classes of respiratory medications during the study period, tiotropium 18 µg once daily administered for up to 4 years in patients with COPD was associated with decreased mortality. Continued follow-up beyond the protocol-defined treatment period appeared to result in a decrease in the magnitude of the benefit. The overall consistency of the results supports a beneficial effect of pharmacotherapy on survival in patients with COPD.

Conflict of Interest Statement: B.C. received \$1,001–\$5,000 from Boehringer Ingelheim, \$1,001–\$5,000 from GlaxoSmithKline, \$1,001–\$5,000 from Aeris, up to \$1,000 from Forrest Pharmaceutical, and \$1,001–\$5,000 from Almirall in consultancy fees; \$10,001–\$50,000 from Boehringer Ingelheim, \$10,001–\$50,000 from GlaxoSmithKline, \$1,001–\$5,000 from Almirall, \$1,001–\$5,000 from Pfizer, and \$5,001–\$10,000 from AstraZeneca for serving on an advisory board; \$5,001–\$10,000 from GlaxoSmithKline, \$5,001–\$10,000 from Boehringer Ingelheim, \$1,001–\$5,000 from AstraZeneca, and \$1,001–\$5,000 from Almirall in lecture fees, more than \$100,001 from GlaxoSmithKline, more than \$100,001 from Boehringer Ingelheim, more than \$100,001 from Aeris, and \$50,001–\$100,000 from Forrest in industry-sponsored grants. M.D. received \$5,001–\$10,000 from Boehringer Pfizer, \$1,001–\$5,000 from GlaxoSmithKline, \$1,001–\$5,000 from Nycomed, \$5,001–\$10,000 from Dompe, \$1,001–\$5,000 from Novartis, and \$1,001–\$5,000 for serving on Chairman Board of Duches Foundation for AstraZeneca. S.K. is a full-time employee of Boehringer Ingelheim. D.L. is a full-time employee of the Boehringer Ingelheim Corporation. S.M. is an employee of Pfizer and holds stock ownership or options in Pfizer. D.P.T. received \$5,001–\$10,000 from Boehringer Ingelheim, \$1,001–\$5,000 from AstraZeneca, \$10,001–\$5,000 from Dey Pharmaceuticals, \$1,001–\$5,000 from Schering-Plough, and \$1,001–\$5,000 from Novartis in advisory board fees; \$5,001–\$10,000 from Boehringer Ingelheim, \$5,001–\$10,000 from AstraZeneca, \$1,001–\$5,000 from Dey Pharmaceuticals, and \$1,001–\$5,000 from GlaxoSmithKline in lecture fees; more than \$100,001 from Boehringer Ingelheim, more than \$100,001 from AstraZeneca, more than \$100,001 from Pfizer, \$50,001–\$100,000 from GlaxoSmithKline, and \$50,001–\$100,000 from Dey in institutional grants.

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Mortality in the 4 Year Trial of Tiotropium (UPLIFT) in Patients with COPD

Bartolome Celli, M.D., Marc Decramer, M.D., Ph.D., Steven Kesten, M.D., Dacheng Liu, Ph.D., Sunil Mehra M.D., Donald P. Tashkin, M.D on behalf of the UPLIFT study investigators*

Online Data Supplement

For internal use only - no further copies allowed**Table E1:** Most common causes of death ($\geq 0.1\%$ of population) during treatment by preferred term as determined by the adjudication committee according to system organ class as determined by the adjudication committee during treatment (a), including vital status information until day 1440 (b), and vital status information until day 1470 (c).

(a) On-Treatment

Preferred Term	Control N = 3,006 IR*	Tiotropium N = 2986 IR*	Rate ratio (95% CI) Tiotropium vs. Control
COPD exacerbation	1.39	1.09	0.79 (0.60, 1.02)
Lung neoplasm	0.76	0.77	1.02 (0.73, 1.43)
Death**	0.41	0.31	0.74 (0.46, 1.21)
Sudden cardiac death	0.26	0.16	0.60 (0.31, 1.15)
Pneumonia	0.21	0.29	1.39 (0.76, 2.52)
Cardiac failure congestive	0.16	0.16	0.99 (0.48, 2.05)
Sudden death	0.14	0.15	1.08 (0.50, 2.33)
Cerebrovascular Accident	0.15	0.13	0.85 (0.39, 1.87)
Myocardial Infarction	0.09	0.10	1.04 (0.40, 2.69)
Colorectal cancer	0.08	0.06	0.79 (0.27, 2.36)
Prostate Cancer	0.03	0.05	1.54 (0.37, 6.44)
Aortic Aneurysm Rupture	0.06	0.03	0.51 (0.17, 1.53)
Pulmonary Embolism	0.03	0.04	1.23 (0.28, 5.50)
Gastric Cancer	0.07	0.01	0.15 (0.02, 1.28)
Metastatic Neoplasm	0.06	0.02	0.37 (0.07, 1.90)
Pancreatic Cancer	0.05	0.02	0.46 (0.08, 2.52)
Sepsis	0.05	0.02	0.46 (0.08, 2.53)

*IR = incidence rate (per 100 patient years), **death where a cause could not be determined

(b) Day 1440

Preferred Term	Control N = 3,006 IR*	Tiotropium N = 2986 IR*	Rate ratio (95% CI) Tiotropium vs. Control
COPD exacerbation	1.38	1.05	0.76 (0.60, 0.97)

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Lung neoplasm	0.64	0.71	1.11 (0.80, 1.54)
Death**	0.55	0.50	0.92 (0.64, 1.33)
Pneumonia	0.18	0.29	1.59 (0.91, 2.79)
Sudden cardiac death	0.23	0.16	0.72 (0.39, 1.31)
Cardiac failure congestive	0.15	0.13	0.87 (0.42, 1.78)
Sudden death	0.17	0.14	0.83 (0.42, 1.64)
Cerebrovascular Accident	0.16	0.13	0.82 (0.40, 1.66)
Myocardial Infarction	0.10	0.10	1.00 (0.43, 2.30)
Colorectal cancer	0.06	0.05	0.85 (0.29, 2.54)
Gastric Cancer	0.06	0.01	0.14 (0.02, 1.16)
Prostate Cancer	0.03	0.04	1.33 (0.30, 5.93)
Aortic Aneurysm Rupture	0.05	0.03	0.60 (0.14, 2.50)
Pulmonary Embolism	0.03	0.04	1.66 (0.40, 6.94)
Metastatic Neoplasm	0.05	0.02	0.40 (0.08, 2.05)
Sepsis	0.04	0.02	0.50 (0.09, 2.72)

IR = incidence rate (per 100 patient years)

(b) Day 1470

Preferred Term	Control N = 3,006 IR*	Tiotropium N = 2986 IR*	Rate ratio (95% CI) Tiotropium vs. Control
COPD exacerbation	1.37	1.09	0.79 (0.62, 1.01)
Lung neoplasm	0.64	0.71	1.11 (0.80, 1.53)
Death**	0.54	0.50	0.94 (0.65, 1.36)
Pneumonia	0.19	0.29	1.52 (0.87, 2.63)
Sudden cardiac death	0.23	0.16	0.72 (0.39, 1.31)
Cardiac failure congestive	0.15	0.14	0.88 (0.44, 1.76)
Sudden death	0.16	0.13	0.83 (0.42, 1.64)
Cerebrovascular Accident	0.15	0.13	0.82 (0.40, 1.66)
Myocardial Infarction	0.10	0.10	1.00 (0.43, 2.30)

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Colorectal cancer	0.06	0.05	0.85 (0.29, 2.54)
Gastric Cancer	0.06	0.02	0.28 (0.06, 1.37)
Prostate Cancer	0.03	0.05	1.66 (0.40, 6.94)
Aortic Aneurysm Rupture	0.05	0.03	0.60 (0.14, 2.50)
Pulmonary Embolism	0.03	0.04	1.66 (0.40, 6.94)
Metastatic Neoplasm	0.05	0.02	0.40 (0.08, 2.05)
Sepsis	0.04	0.02	0.50 (0.09, 2.72)

IR = incidence rate (per 100 patient years)