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Premature Discontinuation of Patients: A Potential Bias in COPD Clinical Trials

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ABSTRACT

Background: Premature discontinuation from clinical trials may bias results against effective therapies.

Methods: We retrospectively reviewed mortality rates in a 6-month, randomized, placebo-controlled trial where tiotropium 18mcg daily was shown to decrease COPD exacerbations. Patients participated for 6 months even if trial medication was prematurely discontinued. Exposure-adjusted incidence rates (IRs) were calculated for 1)randomization–end trial(0–ET); 2)randomization–end trial drug(0–ED); 3)end trial drug–end trial(ED–ET).

Results: Of 1,829 patients (FEV_1=1.04L[36%predicted], age=68years, 99%men), 16%tiotropium and 27%placebo patients prematurely stopped trial medication. Number of fatal events for entire cohort: all cause=62, cardiac=16, lower respiratory=16. IRs for fatal events/100 patient-years were higher in discontinued period [1.9(0–ED) vs. 23.0(ED–ET)(tiotropium) and 1.8 vs. 19.0 (placebo)]. Respective IRs for fatal cardiac events were 0.7 vs. 2.8 (tiotropium) and 0.5 vs. 6.2 (placebo); for fatal lower respiratory events were 0.7 vs. 2.8 (tiotropium) and 0.8 vs. 5.4 (placebo). Rate ratios (tiotropium/placebo) for fatal events were lower in discontinued period: 1.4 vs. 0.5 for cardiac; 0.9 vs. 0.5 for lower respiratory.

Conclusions: Higher IRs of fatal events occurred following premature discontinuation of study medication. Incomplete information from rate ratios occurs from failure to consider outcomes of patients who discontinue early from clinical trials.

KEY WORDS: adverse events, bronchodilators, chronic obstructive pulmonary disease, clinical trials, discontinuation, tiotropium

INTRODUCTION

Randomized, double-blind, controlled clinical trials are the cornerstone of development for pharmaceutical products and devices designed to improve the health of patients afflicted with acute and chronic diseases; however, there are many trial design issues that, when not adequately considered, can lead to unwanted biases.

A potential bias in clinical trials that has not received sufficient consideration is the differential discontinuation rate that may be seen when a highly active compound is compared to no treatment or to a significantly inferior compound. If the effectiveness of a drug is not perceivable by the patient (eg, an improvement in a blood test such as LDL cholesterol) then the degree of benefit of the drug likely has no influence on a patient's decision to continue or discontinue from a clinical trial. However, when the outcome is an important symptom for which patients have cognitive and emotional perceptions then the influence may be profound. An analogy may be drawn to pain studies. If the study is of short duration, such as a few hours or days, the patient may tolerate the discomfort for the study duration. However, over many weeks or months, such a patient may decide that their altruistic reason for participating in a clinical trial has gone beyond an acceptable threshold. A patient perceiving no benefit, yet suffering from continuous pain, may decide to withdraw from a study. If there is a differential discontinuation rate due to such a phenomenon, the conditions exists where the patients who continue in the trial and are receiving the inferior treatment would, on average, be less severely afflicted than patients who are receiving the superior treatment.

Other factors can also affect discontinuation and must be considered when examining this potential bias in the differential discontinuation rate. Patients and health care providers may choose to participate in a clinical trial because of altruism or because of the hope of receiving an active drug that may not otherwise be available;[1] however, once in the trial the patient or their health care provider may choose at any time to discontinue participation.

Tiotropium is the first once-daily, inhaled medication for the treatment of chronic obstructive pulmonary disease (COPD). Clinical trials of tiotropium 18 mcg once daily have consistently demonstrated benefits in lung function, dyspnea, exercise tolerance, health-related quality-of-life, and exacerbations.[2-8] Niewoehner et al. previously reported on a 6-month, randomized, double-blind, placebo-controlled clinical trial assessing the effects of tiotropium 18 mcg once daily on exacerbations of COPD.[8] The trial was conducted in the Veterans Affairs (VA) setting in the United States and demonstrated that tiotropium can reduce COPD exacerbations and associated hospitalizations. The trial was conducted using intention-to-treat principles in which patients were requested to complete follow-up for the full 6 months even if there was premature discontinuation of trial medication. We therefore used the opportunity provided to us with this database to examine how premature discontinuation can influence outcomes such as serious and fatal adverse events.

METHODS

The methods have been described in the original publication and are briefly summarized in the following sections.[8]

Study Design

A parallel-group, double-blind, randomized design was used to study exacerbations of COPD over a 6-month period in COPD patients (trial 205.266). Patients received tiotropium 18 mcg once daily or matching placebo capsules delivered via the HandiHaler dry powder inhalation device in a 1:1 randomization. All patients were receiving care in the VA medical system in the United States and were permitted to continue all previously prescribed respiratory medications other than inhaled anticholinergics. The proportion of patients with at least one exacerbation of COPD and the proportion of patients with at least one hospitalization due to an exacerbation during the six-month trial period represented the co-primary outcomes. The protocol was approved by local institutional review boards and all patients provided written, informed consent.

Study Participants

Inclusion criteria included a clinical diagnosis of COPD, an age of at least 40 years, a smoking history of at least 10 pack-years, and a forced expiratory volume in one second (FEV_1) ≤60% of predicted and ≤70% of the forced vital capacity (FVC).[9,10] Exclusion criteria included asthma, an exacerbation of COPD in the preceding month, myocardial infarction within the prior six months, serious cardiac arrhythmia or hospitalization for heart failure within the prior year, known moderate to severe renal impairment, moderate

to severe symptomatic prostatic hypertrophy or bladder-neck obstruction, or narrow-angle glaucoma.

Procedures

Qualified patients meeting inclusion and exclusion criteria were randomized following a screening visit. Visits were scheduled at 3 and 6 months following randomization. Telephone contacts occurred monthly between clinic visits. Drug compliance was assessed through counts of returned capsules and patients were provided diary cards to record drug use. Spirometry was conducted before and 90 minutes after study drug administration at baseline, 3 months and 6 months.[11] As per intention-to-treat principles, patients were requested to attend all study visits and provide medical information even if study drug was discontinued prior to 6 months.

Exacerbations of COPD

Per the protocol and the published report, an exacerbation of COPD was defined as "a complex of respiratory symptoms (increase or new onset) of more than one of the following: cough, sputum, wheezing, dyspnea, or chest tightness with a duration of at least three days requiring treatment with antibiotics and/or systemic steroids and/or hospital admission."[8] Hospitalizations were confirmed from available medical records. Exacerbations of COPD were reported on an exacerbation-specific case report form. Exacerbation events considered serious, such as hospitalizations (see following section for definition of serious), were also reported on a serious adverse event case report form. Data from both case report form sources were reconciled to insure accuracy and consistency.

Adverse Event Reporting

All serious adverse events were reported by the clinical sites to Boehringer Ingelheim from the time of informed consent to the completion of the trial. Adverse events were defined as any untoward medical occurrence during the trial. A serious adverse event was defined as any untoward medical occurrence during the trial (regardless of a judged relationship to active or placebo capsules) that resulted in death, was immediately life-threatening, resulted in persistent or significant disability, required or prolonged a hospitalization, or was deemed serious for any other reason representing a significant hazard which was comparable to the aforementioned criteria. Serious adverse events were documented on case report forms. Serious adverse events were recorded regardless of whether or not the site considered there to be a relationship to active treatment or placebo capsules. For serious adverse events that were fatal, the start date was recorded as the start of the event that became fatal and not necessarily the date of death. Non-serious adverse events were not systematically collected. The adverse event terms reported by the investigational sites were coded according to the standard medical coding dictionary (Medical Dictionary for Regulatory Activities [MedDRA]) while the trial remained blinded. Modifications to the standard coding conventions (pre-specified prior to trial initiation) included dividing the respiratory system into upper, lower and other as well as combining similar terminology for events of interest such as COPD exacerbations.

Data Analyses

A full description of the data analysis is in the report by Niewoehner et al.[8] Data were analyzed from all patient contacts from the time of inhalation of the first dose of study drug to trial completion.

For adverse events, incidence rates were calculated as the number of patients with an event divided by the person-years at risk.[12] Patients contributed person-time during the time they remained in the study until 30 days following the last dose of study medication or until they experienced the adverse event being assessed. Patients could contribute to multiple events but each event was analyzed separately. If a patient was reported to have more than one occurrence of the identical event, only the time to the first event was utilized.

In the analysis examining the influence of premature discontinuations on adverse events, the analysis of adverse events included the number of patients experiencing the event, the calculated study drug exposure specific for the event, the incidence rate (per 100 patient years), and the rate ratio (tiotropium/placebo) along with the associated 95% confidence intervals. The calculated exposure represents the sum of the time of each patient in the specified time period.

The incidence rate in the tiotropium group divided by the incidence rate in the placebo group defined the rate ratio. Mantel-Haenszel rate ratio estimator was utilized for this analysis and 95% confidence intervals were determined for each event to determine the precision of the estimate.[12]

Incidence rates and rate ratios were calculated for serious and fatal adverse events (total, cardiac and lower respiratory) as well as for COPD exacerbations in the tiotropium and placebo groups using the following timeframes:

a) **Entire trial period (0–ET):** All events occurring over the 6 months from randomization to the end of the clinical trial. For patients who discontinued study drug prior to 6 months and completed the trial, this includes events occurring from the last day of study drug to the end of the trial.

b) **Time on treatment (0–ED):** Events occurring from randomization until the last day of study drug

c) **Time off treatment (ED–ET):** Events occurring from the last day of study drug until the end of the clinical trial (i.e. events occurring in patients who prematurely discontinued).

d) **Time on treatment + 30 days (0–ED30):** Events occurring from randomization until the last day of study drug plus 30 days. The 30 day period immediately following the end of study drug was examined to include any potential residual effects of the drug. Per the protocol, serious adverse events, including deaths, were assigned to a treatment group if they occurred within 30 days of the last dose of study medication.

e) **Time off treatment starting 31 days after study drug (ED30–ET):** Events occurring from 31 days after the last dose of study drug to the end of the clinical

trial (i.e. events occurring in patients who prematurely discontinued that, according to protocol, are not the effect of study drug).

Adverse event data were analyzed for the cardiac and lower respiratory systems because, as expected in this population, these were the most common adverse events. COPD exacerbations were analyzed as this was the primary outcome of the trial.

RESULTS

A total of 1,829 patients were randomized, of which 914 received tiotropium and 915 received placebo. Information at the conclusion of the trial was obtained in approximately 90% of patients. From the tiotropium group, 75 patients (8.2%) withdrew from the trial and 74 patients (8.1%) prematurely discontinued trial drug but completed the trial. From the placebo group, 111 patients (12.1%) withdrew from the trial and 134 patients (14.6%) prematurely discontinued trial drug but completed the trial. In total, trial medication was prematurely stopped by 16.3% of tiotropium treated patients and 26.7% of placebo patients ($p<0.0001$). The major reasons for either prematurely discontinuing trial drug or withdrawing from the trial were worsening of COPD and Other adverse events.

Study Population

The mean age of the population was 68 years with 99% being men (Table 1).[8] The mean FEV_1 was 1.04 L (36% predicted) and the FEV_1/FVC was 48%.[8] Demographic features and baseline respiratory medications were balanced between treatment groups.[8] The FEV_1 percent predicted in tiotropium patients who did not complete study medication but completed the trial was higher than the corresponding placebo group (35.4% vs. 30.9%) suggesting that patients with the lowest lung function preferentially discontinue early in the placebo group. The baseline age, FEV_1 and respiratory medications for the patients who completed the trial, discontinued study drug and continued in the trial and those who prematurely discontinued both study drug and

the trial are listed in Table 2. The proportion of patients receiving respiratory medications at any time (continuous, short-course, or single dosing) during the trial period are displayed in Table 3.

Efficacy Outcomes

As described in the report by Niewoehner et al, the proportion of patients experiencing exacerbations of COPD was reduced in the tiotropium group ($p<0.05$) while the difference in hospitalizations approached statistical significance ($p=0.056$).[8] There were significant reductions in the time to first exacerbation or hospitalization along with reductions in the numbers of events.[8]

Safety

The calculated study drug exposure was approximately 416.1 patient-years in the tiotropium arm and 380.0 patient-years in the placebo arm. A total of 344 patients reported at least one serious adverse event (tiotropium = 174, placebo = 170). The serious adverse events were widely distributed among various organ systems with the majority of events occurring at a low frequency (ie, 1 or 2 patients with a specific event). There were a total of 62 patients who died during the study.

Serious Adverse Events

Exposure adjusted incidence rates for any serious adverse event (SAE) and for cardiac and lower respiratory events are displayed in Table 4. For any serious adverse event, the incidence rates appeared to be similar across groups during all time periods except for an

increase in the tiotropium group in the time off treatment beyond 30 days after the last dose of study drug (ED30–ET).

For cardiac and respiratory adverse events, the incidence rate appeared lower in the tiotropium group relative to the placebo group during study drug treatment (0–ED and 0–ED30) and for the entire trial period (0–ET). There was approximately a two-fold increase in the incidence rate of these events in the placebo group following premature discontinuation of study drug relative to the on-treatment period (cardiac SAEs: 17.4 off treatment [ED–ET] vs. 8.8 on treatment [0–ED]; lower respiratory SAEs: 30.3 off treatment vs. 18.7 on treatment). Similar results were seen relative to the corresponding period with tiotropium (cardiac SAEs: 17.4 off-treatment with placebo vs. 7.9 off-treatment with tiotropium; lower respiratory SAEs: 30.3 off treatment with placebo vs. 17.4 off treatment with tiotropium). Rate ratios (tiotropium/placebo and 95% confidence intervals for all, cardiac and lower respiratory serious adverse events in the tiotropium and placebo group according to onset of event are displayed in Figure 1. Examination of the data suggests that many of these events in the placebo group occur within a 30 day window of cessation of study drug.

Fatal Events

Exposure adjusted incidence rates for any fatal event and for fatal cardiac and lower respiratory events are displayed in Table 5. For any fatal event, the incidence rates werer greater than 10-fold higher after premature cessation of study drug in both groups with most of the difference occurring in the 30 days following cessation of study drug.

For cardiac and respiratory fatal events, the incidence rate appeared similar in the tiotropium and control groups during the study drug treatment. However, the incidence rates were lower with tiotropium for the entire trial period (0–ET). There was approximately a four-fold higher incidence rate of these events in the tiotropium group following premature discontinuation of study drug relative to the on-treatment period (cardiac fatal SAEs: 2.8 off treatment [ED–ET] vs. 0.7 on treatment [0–ED]; lower respiratory fatal SAEs: 2.8 off treatment [ED–ET] vs. 0.7 on treatment [0–ED]). This appeared to be more prominent in the placebo group with an approximately seven-fold increase relative to the on-treatment period (cardiac fatal SAEs: 6.2 off treatment [ED–ET] vs. 0.5 on treatment [0–ED]; lower respiratory fatal SAEs: 5.4 off treatment [ED–ET] vs. 0.8 on treatment [0–ED]). Results were also higher relative to the corresponding period with tiotropium (cardiac fatal SAEs: 6.2 off-treatment with placebo vs. 2.8 off-treatment with tiotropium; lower respiratory fatal SAEs: 5.4 off treatment with placebo vs. 2.8 off treatment with tiotropium). Examination of the data suggests that many of these events in the placebo group occur within a 30 day window of cessation of study drug. The corresponding rate ratios (tiotropium/placebo) and 95% confidence intervals are displayed in Figure 2.

COPD Exacerbations

Exposure adjusted incidence rates for serious and fatal COPD exacerbations are displayed in Table 6. For serious exacerbations, the incidence rate were higher by approximately two-fold in the placebo group after premature cessation of study drug (22.1 off treatment [ED–ET] vs. 12.4 on treatment [0–ED]) whereas it appeared similar in

the tiotropium group (9.2 off treatment [ED–ET] vs. 8.8 on treatment [0–ED]). However, in the tiotropium group, the rate was higher after 30 days following cessation of study drug (26.9 after 30 days beyond off treatment [ED30–ET] vs. 7.9 on treatment + 30 days [0–ED30]). The rate ratio between the two groups (tiotropium/placebo) was lower with tiotropium with the rate ratio being lowest in the period following cessation of study drug (Figure 3).

There were 5 fatal COPD exacerbations in the control group and none in the tiotropium group. However, 4 of 5 events appeared in the period following cessation of study drug with 3 occurring in the 30 day period immediately following cessation of study drug. Rate ratios could not be calculated given the absence of events in the tiotropium group.

DISCUSSION

The completion of a recent tiotropium clinical trial using an intention-to-treat design provided a unique opportunity to evaluate potential biases induced by study designs in standard COPD clinical trials in which patient participation ends upon termination of the intervention. This study was a large, randomized, double-blind, placebo-controlled clinical trial of 6 months duration in which the primary outcome was COPD exacerbations. Patients were permitted to continue use of any previously prescribed respiratory medication other than inhaled anticholinergics. Information at the conclusion of the trial was obtained in approximately 90% of patients. However, premature discontinuation of trial drug occurred in 14.6% of the control group and 8.1% of the tiotropium group who continued to be followed for the complete 6-month study duration. We retrospectively reviewed the exposure-adjusted incidence rates of serious and fatal adverse events and observed a differential effect of the treatment arms dependent of the trial period. For the most common and most relevant events in this population (ie, cardiac and lower respiratory events), there was a higher incidence of events in the post-treatment period. Furthermore, there was a higher risk of experiencing such events in the post-treatment period in the control group relative to the tiotropium group. This differential was higher than that observed in the "on-treatment" period and was most prominent in the immediate 30 days following discontinuation of study medication highlighting the potential impact that such data can have on interpretation of results from clinical trials.

Careful consideration of the design and analyses of clinical trials is mandatory to attain outcomes that can be interpreted in the most unambiguous manner. There are certain types of clinical outcomes that, by their nature, minimize potential complexities in interpretation. Trials of acute bronchodilators often involve direct observation for the entire treatment period and one can reasonably expect to attain complete follow-up with minimal biases introduced.[13,14] The study of chronic diseases such as COPD which often have complex outcomes become much more problematic. In studies extending over months or years, the patient resides in an uncontrolled setting (ie, their home) and are subject to social and occupational environments that result in exposure to a host of uncontrolled influences. Nevertheless, with large enough sample sizes, these factors should be randomly and equally distributed between study groups. Yet, when there is a clear differential in the effectiveness of one treatment arm over time, other unanticipated biases may occur. These biases could influence a primary outcome such as lung function, symptom improvement, worsening of the underlying disease, or mortality.

How might such a bias occur? In the case of a highly effective drug matched against an ineffective intervention, this bias can occur when patients in the active group are more likely to complete the trial than those in the non-active group.[3-5] This can be expected when an outcome is of importance to the patient. In the case of COPD, this could include improvements in dyspnea and exercise tolerance and a reduction in exacerbations.[15] The disease is also characterized by periodic acute and sub-acute worsenings (ie, exacerbations).

Although patients enter for altruistic reasons, there is also hope of receiving an active drug that could improve their underlying condition.[1] Failure to meet the expectation for improvement along with the continued limitations invoked by COPD may lead to premature discontinuation, particularly in longer-term trials. For example, in a 3-year trial of inhaled steroids in COPD, discontinuations exceeded 40%.[16] Furthermore, the patients could experience sub-acute or acute worsening of their disease which may lead to the investigator or the patient deciding that participation should be terminated prematurely. While such an event should be recorded as worsening of underlying COPD or a COPD exacerbation, it may simply be viewed as withdrawing consent or termination for other reasons. The situation may further be exaggerated in the case of a marketed product where the patient and health care provider know that an active and efficacious medication may be purchased.

In the case of tiotropium, multiple clinical trials indicate that improvements in dyspnea, exercise tolerance, health-related quality of life, and exacerbations can reasonably be expected.[3-8] However, in previous clinical trials with tiotropium of at least 6 months duration, patient participation ended with the last day of study drug (either prematurely or because they completed the full course of study drug treatment).[3-5] While investigators were asked to report any serious adverse events in the 30 days following the last day of study drug, follow-up visits were not part of the trial protocols. In each of these reports, the tiotropium treated group was associated with a lower frequency of premature discontinuations.[3-5] The present study is the first reported tiotropium trial

where follow-up information in patients who prematurely discontinued study medication was systematically collected.[8]

There were several observations worthy of further discussion. First, it is hypothesized that patients who discontinue early, often do so because they have more severe underlying disease, are more predisposed to clinically important worsening of their condition, and are at higher risk of dying. This is indeed the case based on the analysis. Examination of the control group indicated multi-fold increases in the incidence rate of death, serious respiratory and serious cardiac events. Second, if the hypothesis is true, it may be expected that such events would preferentially surface shortly after prematurely discontinuing thereby suggesting an association. Again, the data in the control group support this conjecture. Finally, it is surmised that this finding would preferentially be observed in the control group in the case of a comparison to a highly active compound. This observation is particularly notable in regards to one of the more important clinical outcomes and, for this trial, the primary outcome. Serious lower respiratory events including exacerbations occurred with a lower incidence rate in the tiotropium group during study drug treatment, but this difference was exaggerated during the period following early discontinuation. Furthermore, there was no difference in mortality due to lower respiratory events during the treatment period but a difference appeared during the post-treatment period which was most prominent during the initial 30 days. Indeed, for fatal exacerbations, there was 1 case in the control group vs. none in the tiotropium group during treatment but at the end of the trial, there was 5 in the control group vs. 0 with tiotropium.

The implications of these observations are highly significant. Results from clinical trials with highly efficacious benefits for important clinical outcomes may underestimated due to the differential discontinuation rates (ie, "healthier survivor" effect) in the control group if follow-up data is not collected on patients who prematurely discontinue study medication. In the worst case, imbalances may be observed in important adverse events, such as fatal events, in the disease under study that are unfavorable for the active treatment group. In other words, there may be a greater number of deaths in the active arm of a highly effective intervention due to early discontinuation of the most severely afflicted patients in the control group who are destined to die in the short term. Inaccurate conclusions could be drawn that could diminish or eliminate the use of effective treatments in serious chronic diseases.

Calverley et al reported the determinants of patient withdrawal from the Inhaled Steroids in Obstructive Lung Disease (ISOLDE) study.[17] ISOLDE was a double-blind, placebo-controlled, randomized clinical trial evaluating the effect of inhaled steroids on the rate of decline of FEV_1.[16] More patients in the placebo group withdrew prematurely due to frequent courses of oral corticosteroids, which was most prominent in patients with FEV_1 below 50% of predicted normal at entry into the study.[17] However, this analysis was based only on data obtained while patients received study drug, as patients who stopped study drug were withdrawn from the trial. A subsequent publication of follow-up of causes of death in the ISOLDE trial has appeared in abstract

form only.[18] Deaths were checked against centralized records in England and Scotland. The crude incidence of death was higher in patients withdrawn from the study.

The present tiotropium study has the advantage of pre-specification of collection of follow-up data in patients who prematurely discontinued trial medication. While data was not obtained in approximately 10% of discontinued patients, the availability of follow-up data in 90% can be considered high in light of the disease and duration of the trial. A potential limitation in the present study is that the analysis is retrospective. We have noted that there are occasions when the last day of study drug was recorded as the day prior to an adverse event and the event would therefore be considered to have occurred within the prematurely discontinued period. Retrospectively, it is difficult to be certain whether such events should be included in the data for the active drug treatment period. A sensitivity analysis suggests that the impact of this is small and does not alter the conclusions of this report. A strength of the study is that the trial was conducted entirely in the VA medical system. The VA system is a relatively closed system and has electronic medical records, which increased the reliability of the data and decreased the likelihood of missing information. Patients tend to stay within the system although they have the option of seeking health care outside of the VA system. In addition, hospital discharge records were aggressively sought and reviewed while the study team remained blinded to treatment allocation.

In summary, in a large, randomized, double-blind, controlled trial of 6-months duration examining exacerbations of COPD, important clinical differences in serious adverse

events including fatal events were observed depending on time following premature discontinuation of study medication. A priori inclusion in the protocol of collection of follow-up data for discontinued patients led to the observation of an overall higher incidence of cardiac and respiratory serious events during the post-treatment period as well as the observation of differences between treatment groups in the incidence of these events in favor of the active drug (tiotropium) during the post-treatment period. The post-treatment period data suggest that the benefits of tiotropium would be underestimated without inclusion of the data. These observations suggest that all long-term trials in COPD should consider the impact of early discontinuations of trial medication when the active arm is anticipated to have significant clinical benefits. While complete follow-up of patients who stop study drug is desirable, the challenges involved in trying to obtain and interpret follow-up data should be considered when designing clinical trials.

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TABLE 1 Baseline characteristic of the tiotropium and placebo groups.

	Tiotropium	**Placebo**
	(n = 914)	**(n = 915)**
Men, n (%)	898 (98)	904 (99)
Mean age ± SD, (years)	67.6 ± 8.7	68.1 ± 8.5
White, N (%)	847 (93)	823 (90)
Current smoker (%)	263 (29)	272 (30)
Smoking status		
Current smoker, n (%)	263 (29)	272 (30)
Mean pack-year history ± SD	67.4 ± 35.4	69.4 ± 36.6
Duration of COPD ± SD (years)	12.2 ± 10.4	11.9 ± 10.5
Mean baseline spirometry ± SD		
FEV_1 (L)	1.04 ± 0.40	1.04 ± 0.40
FEV_1 (% predicted)	35.6 ± 12.6	35.6 ± 12.6
FEV_1/FVC (%)	47.9 ± 11.5	47.7 ± 11.1
Medications for COPD, n (%)		
Inhaled β-agonist		
Any	851 (93)	864 (94)
Nebulized	237 (26)	234 (26)
Long-acting	346 (38)	351 (38)
Ipratropium bromide		
Any	735 (80)	728 (80)
Nebulized	138 (15)	157 (17)

Corticosteroids		
Inhaled	559 (61)	531 (58)
Oral	94 (10)	97 (11)
Theophylline	141 (15)	118 (13)
Leukotriene antagonist	59 (6)	53 (6)
Home oxygen	259 (28)	272 (30)

Table 1 is adapted from Niewoehner DE, Rice K, Cote C, Paulson D, Cooper AD Jr, Korducki L, Cassino C, Kesten S. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator. *Ann Intern Med* 2005; 143:317-326. Copyright 2005, American College of Physicians.

TABLE 2 Baseline age, FEV_1 (mean (SD)) and respiratory medications (proportion of population) according to treatment group and completion/discontinuation status.

	Completed		Discontinued trial*		Discontinued study drug**	
	tiotropium	placebo	tiotropium	placebo	tiotropium	placebo
	n=762	n=670	n=75	n=111	n=74	n=134
Age	68 (9)	68 (9)	67 (9)	67 (9)	69 (8)	70 (9)
FEV_1 (L)	1.05 (0.40)	1.07 (0.39)	0.96 (0.42)	1.02 (0.40)	0.99 (0.40)	0.89 (0.39)
FEV_1 (% predicted)	36 (12)	37 (12)	33 (13)	35 (12)	35 (15)	31 (13)
Respiratory medication (%)						
Anticholinergic	79	77	84	84	89	87
Long-acting beta-agonist	39	38	28	34	39	45
Inhaled steroid	61	57	65	62	74	68
Theophylline	16	12	9	15	13	23
Oral steroid	10	9	9	8	14	23

Oxygen	25	25	31	30	31	40

* no follow-up after discontinuation; **followed for duration of trial after drug discontinuation

TABLE 3 Respiratory medications (proportion of population) used at any time during the trial period according to treatment group and completion/discontinuation status.

	Completed		Discontinued trial*		Discontinued study drug**	
	tiotropium	placebo	tiotropium	placebo	tiotropium	placebo
	n=762	n=670	n=75	n=111	n=74	n=134
Respiratory medication (%)						
Anticholinergic	5	6	24	32	73	86
Long-acting beta-agonist	47	45	28	34	50	54
Inhaled steroid	61	57	45	51	72	75
Theophylline	17	14	5	10	22	15
Oral steroid	15	15	11	17	31	38
Oxygen	29	31	31	26	45	52

* no follow-up after discontinuation; **followed for duration of trial after drug discontinuation

TABLE 4. Serious adverse events: Exposure adjusted incidence rates (per 100 patient years) of total (any), cardiac and lower respiratory serious adverse events (SAEs) in the tiotropium and placebo group according to onset of event.

		Tiotropium (n=914)			Placebo (n=915)			Risk Ratio (95% CI)
	Onset	**n**	**Exposure**	**Rate**	**n**	**Exposure**	**Rate**	**(tiotropium/placebo)**
Any SAE	0-ET	174	464	37.5	170	456	37.3	1.01 (0.82, 1.24)
	0-ED	146	387	37.8	129	355	36.3	1.04 (0.82, 1.32)
	ED-ET	28	77	36.3	41	101	40.6	0.89 (0.55, 1.45)
	0-ED30	162	449	36.1	156	428	37.3	0.97 (0.78, 1.21)
	ED30-ET	12	15	79.5	14	38	36.8	2.16 (1.00, 4.67)
Cardiac SAE	0-ET	38	512	7.4	54	495	10.9	0.68 (0.45, 1.03)
	0-ED	30	411	7.3	33	374	8.8	0.83 (0.51, 1.36)
	ED-ET	8	101	7.9	21	121	17.4	0.45 (0.20, 1.03)
	0-ED30	33	483	6.8	48	446	10.8	0.64 (0.41, 0.99)
	ED30-ET	5	29	17.3	6	49	12.2	1.42 (0.43, 4.65)

Resp (lower) SAE	0-ET	80	496	16.1	103	480	21.4	0.75 (0.56, 1.01)
	0-ED	64	4	15.8	69	368	18.7	0.85 (0.60, 1.19)
	ED-ET	16	92	17.4	34	112	30.3	0.58 (0.32, 1.04)
	0-ED30	72	474	15.2	90	437	20.6	0.74 (0.54, 1.01)
	ED30-ET	8	22	35.9	13	44	29.6	1.21 (0.50, 2.93)

CI=confidence interval; n=number of events; 0–ET=randomization to end of trial (entire trial period); 0–ED=randomization to end of drug (time on treatment); ED–ET=end of drug to end of trial (time off-treatment); 0–ED30=randomization to end of drug (time on treatment) + 30 days; ED30–ET=from 31 days after end of drug to end of trial

TABLE 5. Fatal events: Exposure adjusted incidence rates (per 100 patient years) of total (any), cardiac and lower respiratory fatal events in the tiotropium and placebo group according to onset of event.

		Tiotropium (n=914)			Placebo (=915)			Risk Ratio (95% CI)
	Onset	**n**	**Exposure**	**Rate**	**n**	**Exposure**	**Rate**	**(tiotropium/placebo)**
Any Fatal Event	0-ET	31	516	6.0	31	506	6.1	0.98 (0.60, 1.61)
	0-ED	8	416	1.9	7	380	1.8	1.04 (0.38, 2.88)
	ED-ET	23	100	23.0	24	126	19.0	1.21 (0.68, 2.14)
	0-ED30	22	490	4.5	19	454	4.2	1.07 (0.58, 1.98)
	ED30-ET	9	26	34	12	52	23.1	1.47 (0.62, 3.49)
Cardiac Fatal	0-ET	6	523	1.2	10	509	2.0	0.58 (0.21, 1.61)
	0-ED	3	416	0.7	2	380	0.5	1.37 (0.23, 8.20)
	ED-ET	3	107	2.8	8	129	6.2	0.45 (0.12, 1.70)
	0-ED30	3	491	0.6	6	455	1.3	0.46 (0.12, 1.85)
	ED30-ET	3	32	9.4	4	54	7.4	1.26 (0.28, 5.65)

Resp (lower) Fatal	0-ET	6	522	1.2	10	509	2.0	0.59 (0.21, 1.61)
	0-ED	3	416	0.7	3	380	0.8	0.91 (0.18, 4.52)
	ED-ET	3	106	2.8	7	129	5.4	0.52 (0.14, 2.02)
	0-ED30	3	491	0.6	7	455	1.5	0.40 (0.10, 1.54)
	ED30-ET	3	31	9.7	3	54	5.5	1.75 (0.36, 8.71)

CI=confidence interval; n=number of events; 0–ET=randomization to end of trial (entire trial period); 0–ED=randomization to end of drug (time on treatment); ED–ET=end of drug to end of trial (time off-treatment); 0–ED30=randomization to end of drug (time on treatment) + 30 days; ED30–ET=from 31 days after end of drug to end of trial

TABLE 6. Exacerbations of COPD: Exposure adjusted incidence rates (per 100 patient years) of serious and fatal exacerbations of COPD in the tiotropium and placebo group according to onset of event.

		Tiotropium (n=914)			Placebo (n=915)			Risk Ratio (95% CI)
	Onset	**n**	**Exposure**	**Rate**	**n**	**Exposure**	**Rate**	**(tiotropium/placebo)**
Serious	0-ET	45	508	8.9	72	489	14.7	0.60 (0.41, 0.87)
	0-ED	36	410	8.8	46	371	12.4	0.71 (0.46, 1.10)
	ED-ET	9	98	9.2	26	117	22.1	0.42 (0.19, 0.89)
	0-ED30	38	482	7.9	61	442	13.8	0.57 (0.38, 0.86)
	ED30-ET	7	26	26.9	11	47	23.5	1.15 (0.45, 2.96)
Fatal	0-ET	0	523	0	5	510	1.0	N/A[†]
	0-ED	0	416	0	1	380	0.3	N/A[†]
	ED-ET	0	107	0	4	130	3.1	N/A[†]
	0-ED30	0	491	0	3	455	0.7	N/A[†]
	ED30-ET	0	32	0	2	55	3.7	N/A[†]

[†]No patients in the tiotropium group had a fatal COPD exacerbation

CI=confidence interval; n=number of events; 0–ET=randomization to end of trial (entire trial period); 0–ED=randomization to end of drug (time on treatment); ED–ET=end of drug to end of trial (time off-treatment); 0–ED30=randomization to end of drug (time on treatment) + 30 days; ED30–ET=from 31 days after end of drug to end of trial

LEGEND TO FIGURES

FIGURE 1: Rate ratios and 95% confidence intervals of total (any), cardiac and lower respiratory serious adverse events (SAEs) in the tiotropium and placebo group according to onset of event.

Figure 1

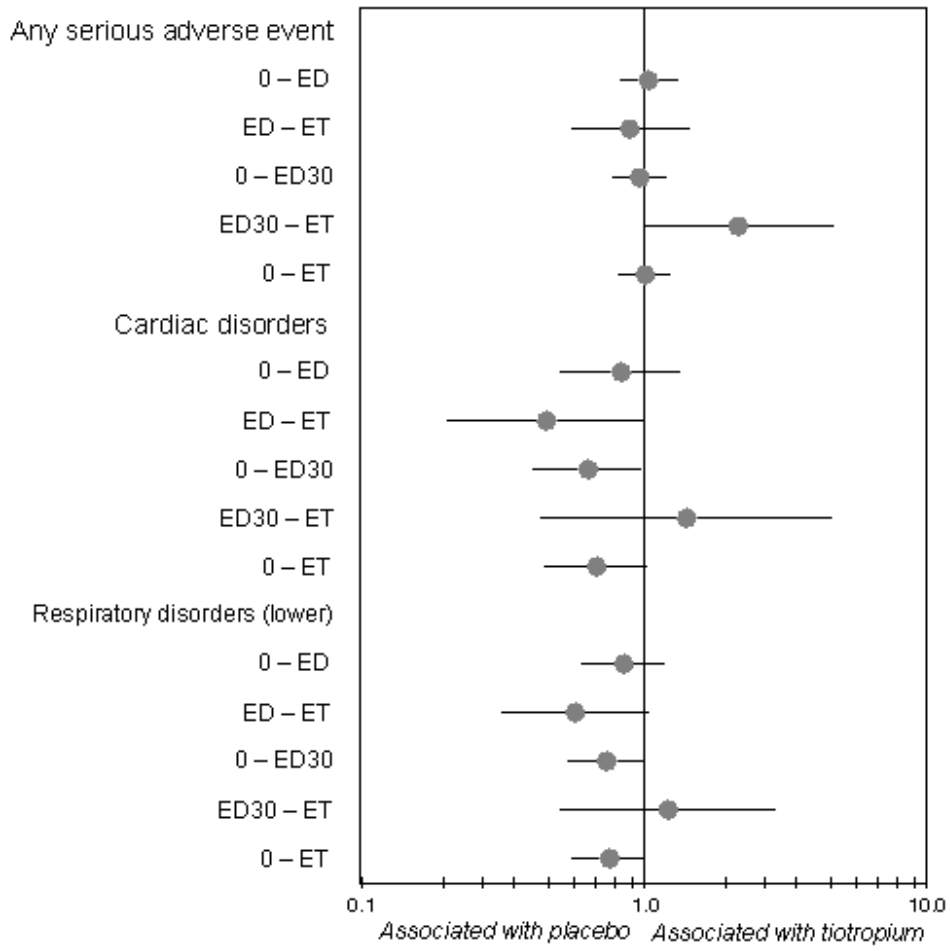

FIGURE 2: Rate ratios and 95% confidence intervals of total (any), cardiac and lower respiratory fatal in the tiotropium and placebo group according to onset of event.

Figure 2

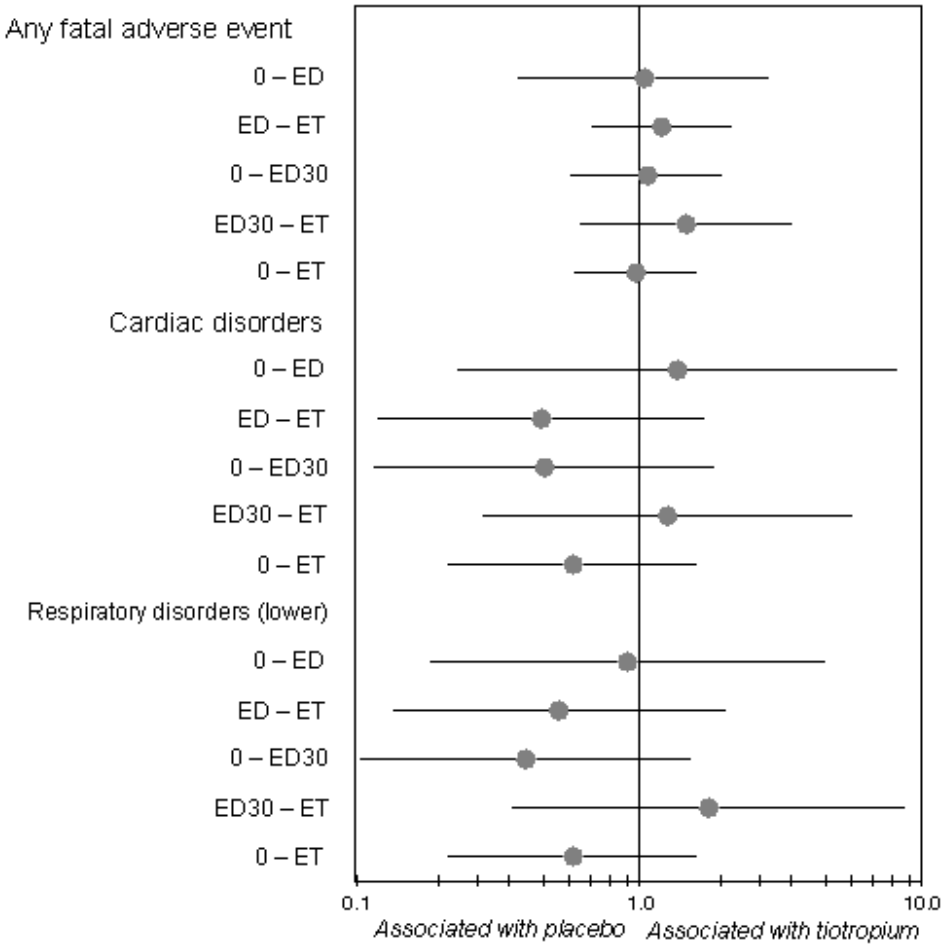
Any fatal adverse event
0 – ED
ED – ET
0 – ED30
ED30 – ET
0 – ET
Cardiac disorders
0 – ED
ED – ET
0 – ED30
ED30 – ET
0 – ET
Respiratory disorders (lower)
0 – ED
ED – ET
0 – ED30
ED30 – ET
0 – ET
0.1
1.0
10.0
Associated with placebo
Associated with tiotropium

FIGURE 3: Rate ratios and 95% confidence intervals of COPD exacerbations reported as serious adverse events in the tiotropium and placebo group according to onset of event.

Figure 3