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Long-Term Efficacy of Tiotropium in Relation to Smoking Status in the UPLIFT Trial

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Abstract
Background: UPLIFT, a 4-year trial of tiotropium in COPD, allowed for assessment of smoking status on long-term responses to maintenance bronchodilator therapy.
Methods: 5993 patients were randomized (tiotropium/placebo). Lung function, St. George's Respiratory Questionnaire (SGRQ), exacerbations and adverse events were followed. Patients were characterized as continuing smokers (CS), continuing ex-smokers (CE), or intermittent smokers (IS) based on self-reporting smoking behavior.
Results: 60%, 14% and 26% of patients were CE, CS, and IS. The rate of FEV_1 decline for placebo patients was most rapid in CS (-51±4, -36±2, and -23±2ml/yr in CS, IS, and ES respectively). Tiotropium did not alter FEV_1 decline, but was associated with significant improvements in pre&post-bronchodilator FEV_1 over placebo that persisted throughout the 4-year trial for each smoking status (pre-bronchodilator: 125, 55, and 97 ml at 48 months, in CS, IS, CE, respectively; p<=0.0003). Tiotropium reduced exacerbation risk in CS (HR(95%CI) 0.81 (0.68-0.97)), in CE (0.86 (0.79-0.93)) and trended towards significance in IS (0.89 (0.80-1.01)). At four years, SGRQ for tiotropium patients improved the most in CS (-4.62 units, p=0.0006) and the least in IS (-0.54 units, p=0.55), compared with control.
Conclusion: Tiotropium provided long-term benefits irrespective of smoking status, although differences among categories were observed.

Key Words: COPD; FEV_1 rate of decline; smoking behavior; tiotropium

This trial has been registered with ClinicalTrials.gov (number NCT 00144339)
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Introduction

The relation of smoking behavior and long-term responses to maintenance bronchodilator therapy has not been thoroughly evaluated. Comparing the efficacy of the long-acting anticholinergic bronchodilator, tiotropium, in a 3-month study between 80 smokers and 224 ex-smokers with chronic obstructive pulmonary disease (COPD), Moita et al. (1) previously reported twice as large a placebo-adjusted improvement in pre-bronchodilator forced expired volume in 1 second (FEV_1) in the smokers (138 ml) than the ex-smokers (66 ml), although the difference in the response to tiotropium between the two smoking groups was not statistically significant. In contrast, in a pooled analysis, stratified by smoking status, of seven clinical trials in which the short-acting anticholinergic bronchodilator, ipratropium, was compared with a $beta_2$-agonist over a 90-day treatment period in a total of 1,836 subjects with moderately severe COPD, the improvement in baseline lung function in the ipratropium-treated patients was found to be more marked in ex-smokers than current smokers (2).

The 4-year multinational placebo-controlled trial of tiotropium versus placebo in 5,993 subjects with COPD (UPLIFT®, Understanding Potential Long-Term Improvements in Function with Tiotropium) (3) provided an opportunity to assess more fully the potential relationship between smoking status and both lung function and patient-reported outcomes of maintenance therapy with a long-acting muscarinic antagonist over an extended period of time in a large group of continuing smokers, intermittent smokers, and ex-smokers with COPD, taking into account the potentially confounding influence of concomitant respiratory medications.

Methods

Study Design
UPLIFT® was a 4-year, randomized, placebo-controlled clinical trial in 5,993 patients with COPD. The methods have been previously published in detail as have the main results (3, 4). In brief, key inclusion criteria consisted of: 40 years of age or greater, smoking history of at least 10 pack-years, post-bronchodilator forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio of 0.70 of predicted or less, and post-bronchodilator FEV_1 of 70% predicted or less. Key exclusion criteria included: COPD exacerbation within 4 weeks prior to screening, respiratory infection within 4 weeks prior to screening, history of asthma, prior pulmonary resection, and use of supplemental oxygen for more than 12 hours per day. The protocol was approved by the local ethics committees and all patients provided written informed consent.

Patients were randomized to receive either tiotropium or placebo. All patients were permitted to use other maintenance respiratory medications throughout the trial with the exception of inhaled anticholinergics. The co-primary endpoints were the annual rate of change of both pre- and post-bronchodilator FEV_1 from 30 days after randomization through 48 months.

A smoking cessation program was offered to all patients after consent and prior to randomization. Of 1,825 patients who were smoking at the time of screening, 150 reported no smoking at baseline, possibly as a consequence of the smoking cessation program that was offered to all eligible participants prior to randomization. Of 4,167 patients who reported abstinence from smoking at screening, 97 reported having relapsed to smoking at randomization. For the analysis described herein, patients were also grouped according to on-trial smoking status, i.e., as to whether they were continuing smokers, continuing ex-smokers, or intermittent smokers during the course of the study. Continuing smokers consisted of patients who were recorded as smoking at baseline and having continued to smoke at all clinic visits. Continuing ex-smokers consisted of patients who were recorded as having quit smoking prior to randomization and having maintained smoking abstinence at all clinic visits. Intermittent smokers were defined as subjects who changed their smoking behavior from randomization on at least one clinic visit.

Statistical Analysis
The decline of pulmonary function over time was analyzed with random coefficient regression in which the FEV1 changed linearly after 30 days for each patient. Individual intercepts and slopes were random following bivariate normal distributions with different means for each treatment group, and a common covariance matrix. The same model was used for SGRQ decline over time (from 6 months until completion of the study). All patients who underwent randomization and received study drug and who had at least three post-randomization measurements of pulmonary function (at least two for SGRQ) were used in the analyses of decline. SGRQ values from Turkey were excluded due to an error in the translation of the questionnaire.

The values of pulmonary function tests at specific time points throughout the study were modeled using mixed model repeated measures analysis of covariance with a unstructured covariance matrix. The same restriction to subjects with three post-randomization measurements of pulmonary function (two for SGRQ) as in the analyses of decline was used.

Cox regression was used for the time to event endpoints of exacerbations and mortality. For exacerbations and exacerbations leading to hospitalization, the number of events and event days were compared between the study groups with relative risks through the use of Poisson regression with correction for overdispersion.

Analyses were performed with SAS software, version 8.2 (SAS Institute, Cary, North-Carolina). All reported p-values are two-sided and not corrected for multiple testing. Details of the statistical analysis plan are described in the report by Tashkin et al[3].

Results

Patient Demographics
A total of 5992 randomized COPD patients were included in the analysis (Figure 1). With respect to on-trial smoking status, information is available on a subset of 5,925 patients. At baseline, 70% of the patients were ex-smokers and 30% were active smokers. Over the course of the trial, 60% of the patients were continuing ex-smokers, 14% continuing smokers and 26% were intermittent smokers (Table 1). Of the ex-smokers at baseline, 85% in the placebo group and 83% in the tiotropium group remained ex-smokers, while 14% in the placebo group and 16% in the tiotropium group had at least one clinic visit in which they reported smoking. Of the patients who were active smokers at baseline, 48% in the placebo group and 47% in the tiotropium group remained smokers, while 50% in the placebo group and 52% in the tiotropium group had at least one clinic visit in which they reported not-smoking. A greater proportion of women than men were intermittent smokers. Mean age varied between 61 and 66 years for the different smoking categories. GOLD Stage II and III patients accounted for between 89 and 93% of the patient population in each smoking status category.

While for most demographic variables the distribution between tiotropium-treated and placebo-treated patients by smoking category was generally similar, notable disparities existed in relation to both gender and baseline disease severity (Table 1). A greater percentage of continuing smokers randomized to receive tiotropium were male (72%) than the percentage of continuing smokers randomized to receive placebo (62% male). Continuing ex-smokers differed in the percentage of individuals in GOLD stages II and III by randomization group. For continuing ex-smokers randomized to placebo, 41% and 48% were in GOLD stages II and III at baseline, respectively. For continuing ex-smokers randomized to tiotropium, 45% and 44% were in GOLD stages II and III at baseline, respectively.

At baseline pre-and post bronchodilator FEV_1 was lowest in continuing ex-smokers (Table 1). Similarly, baseline pre-and post-bronchodilator forced vital capacity (FVC) and slow vital capacity (SVC) were lowest in continuing ex-smokers. All three categories of smokers showed a similar degree of reversibility (22-24% improvement in FEV_1) following serial administration of 4 actuations of ipratropium and albuterol. For each treatment group, post-bronchodilator FEV_1/FVC was between 42% and 46% of predicted. Mean SGRQ total scores at baseline ranged between 44 and 49 across all smoking groups. Continuing smokers had the highest (worst) SGRQ scores.

Lung Function Outcomes

Irrespective of treatment assignment, continuing smokers had the most rapid rate of FEV_1 decline and the continuing ex-smokers the slowest rate of decline with the intermittent smokers exhibiting an intermediate decline. However, for each smoking category the rate of lung function decline (FEV_1) showed similar differences between the tiotropium and control arms (Table 2; Figure 2). Although the primary endpoint in UPLIFT was rate of change in FEV_1 from 30 days through 48 months post-randomization and was similar between treatment groups within each of the three smoking behaviour categories, significant improvements in lung function (FEV_1, FVC and SVC) were observed with tiotropium compared to the control group within each of the three smoking behaviour categories throughout the trial (Table 3, Figures 2 & 3 and online depository Figure 2). The improvements in the continuing smoking group were numerically larger than in either the ex-smoking or the intermittent smoking group. This was evident at both one month and 48 months after the initiation of treatment (Table 3).

Exacerbations

The hazard ratios (tiotropium/control) for time to first exacerbation indicated that tiotropium was associated with a reduced risk of an exacerbation by 19% and 14% in continuing smokers and ex-smokers, respectively (p=0.02 and p=0.0002, respectively) and, to a lesser extent, in intermittent smokers (11%, p=0.062) (Table 4). Tiotropium also was associated with a tendency towards reduced exacerbation frequency irrespective of smoking status. The results were statistically significant in continuing ex-smokers in whom the reduction was 16% compared with placebo. Continuing ex-smokers and intermittent smokers were 13% and 18% less likely to experience an exacerbation leading to hospitalization, respectively, when treated with tiotropium (p=0.036 for both), although there was no difference in continuing smokers (Table 4).

Health-Related Quality of Life

Tiotropium was associated with improved SGRQ scores at both 6 and 48 months in both continuing smokers and continuing ex-smokers, the effect being largest in the continuing smokers (Table 5). There appeared to be a consistency in the magnitude of differences among domains within smoking behaviour groups. Intermittent smokers had the smallest differences numerically with no statistical significance at 48 months; however, larger differences were observed at time points prior to 48 months (range for total score: -1.35 to -2.17).

Mortality

Mortality was assessed using three approaches: (a) during the actual treatment period (1st dose to last dose + 30 days), (b) during the protocol defined treatment period (4 years) including collection of vital status information from prematurely discontinued patients, and (c) at the conclusion of a 30 day period after the protocol defined treatment period (4-years + 30 days). Vital status collection was complete for 95% of patients at 4 years and only 75% at the end of the subsequent 30-day washout. For each method of assessing mortality, sustained smokers had the highest mortality rate followed by continuing ex-smokers and then intermittent smokers (Table 6). The hazard ratios (tiotropium/control) and 95% confidence intervals, also displayed in Table 6, indicate reductions in mortality in continuing ex-smokers and intermittent smokers related to tiotropium that were statistically significant in the continuing ex-smokers (19% risk reduction) both on treatment and during the protocol-defined treatment period (vital status 4-years).

However, no benefit of tiotropium on mortality was evident in the continuing smokers or the intermittent smokers.

Discussion

While the efficacy of inhaled corticosteroid therapy has been shown to be impaired by smoking in both COPD and asthma (5-11) and theophylline clearance is increased in smokers, potentially affecting efficacy and toxicity (12), the influence of smoking behavior on the long-term response to inhaled bronchodilator therapy in COPD has not been well-studied. The sparse publications that have addressed this issue are mainly limited to short-term, 3-month studies involving anticholinergic bronchodilators and have yielded somewhat conflicting findings, as described above (1,2); one of these studies showed a substantially, although not significantly, greater numeric response to tiotropium in trough FEV_1 in continuing smokers than ex-smokers (1), while the other showed a more marked trough FEV_1 response to ipratropium in ex-smokers than current smokers (2).

The UPLIFT trial provides a unique opportunity to re-examine this issue in view of its 4-year duration and the large scope of the trial that included nearly 850 patients who continued to smoke throughout the trial and over 3,500 ex-smokers who maintained abstinence from smoking throughout the entire study period. Moreover, the percentage of patients within these smoking status categories was well-balanced at least between the two treatment groups overall, although some imbalance was observed in gender and disease severity: continuing ex-smokers were slightly older, included a higher proportion of men and displayed more severe airflow obstruction than continuing smokers, the intermittent smokers exhibiting intermediate characteristics.

The sub-analysis by smoking status demonstrated that continuing smokers showed a worse outcome than continuing ex-smokers in terms of the rate of decline in both pre- and post-bronchodilator FEV_1 with intermittent smokers demonstrating intermediate outcomes, irrespective of maintenance anticholinergic therapy, consistent with previous findings from the Lung Health Study (13, 14). On the other hand, tiotropium was associated with consistently significant improvements in lung function compared to the control arm over the course of the 4-year study in all smoking behavior categories, except for a more modest and non-significant improvement in post-bronchodilator FEV_1 in the intermittent smokers at 4 years. Interestingly, consistent with the earlier findings of Moita et al. (1), the tiotropium-related improvement FEV_1 was numerically greater in the continuing smokers than the ex-smokers at trough and even more so when examined after the administration of study drug and 4 inhalations of albuterol and ipratropium (Table 3). However, the results of the study by Moita et al may not necessarily be comparable to the results of the UPLIFT trials due to possible differences in the proportion of subjects using concomitant medications in the two studies. It is tempting to speculate that the apparently greater bronchodilator effect of tiotropium in the continuing smokers may be related to counteraction by the anticholinergic bronchodilator against the well-known bronchoconstrictor effects of cigarette smoke that are believed to be mediated via reflex cholinergic pathways.

Apparent benefits of tiotropium compared to placebo were noted in both the risk for developing an exacerbation and the frequency of exacerbations across all smoking status categories, although these benefits achieved statistical significance only in the continuing ex-smokers. Similarly, tiotropium appeared to be associated with a reduced risk for exacerbations leading to hospitalization across the three smoking categories, but the difference from placebo was

significant only among the continuing ex-smokers and intermittent smokers. Over the course of the trial, tiotropium also was associated with improvements in health-related quality of life that were significant in both the continuing smokers and continuing ex-smokers, although the magnitude of the benefit was numerically greatest in the continuing smokers, among whom the benefit exceeded the threshold for a minimal clinically important difference (≥4 units total SGRQ score). Taken together, these findings suggest a beneficial association of tiotropium with both lung function and patient-reported outcomes in patients with moderate to severe COPD in all subgroups of smoking behavior, but with different intensity, over the 4-year course of the study.

Continuing smokers exhibited a higher all-cause mortality rate than subjects in the other smoking categories both on-treatment and over the protocol-defined treatment period, consistent with previous data from the Lung Health Study demonstrating a beneficial effect of smoking cessation and continuing abstinence, as well as of intermittent periods of smoking abstinence, in reducing 14.5-year mortality, including all-cause mortality and mortality due to coronary heart disease, cardiovascular disease and lung cancer, in subjects with mild to moderate COPD (15). Tiotropium was associated with significantly reduced mortality in the continuing ex-smokers while on-treatment and during the 4-year treatment period with a trend toward a reduction in mortality in the intermittent smokers during the same periods of the study. However, no benefit of tiotropium on all-cause mortality was apparent in the continuing smokers. The latter finding might reflect the higher risk of continuing smokers for fatal cardiovascular events for which a long-acting bronchodilator might not offer sufficient protection.

There are several limitations to the current study. First, notable disparities in baseline characteristics between tiotropium-treated and placebo-treated patients were observed within the various categories of on-trial smoking behavior. These imbalances were strongest with respect to gender and baseline disease severity. The possible effects of gender and disease severity on tiotropium effects in UPLIFT are currently under investigation. Second, responses to tiotropium may have been influenced by concomitant therapy with inhaled corticosteroids or theophylline, the potentially confounding effects of which may have been altered by smoking. Third, smoking status was not verified at the various clinic visits by objective measures, such as exhaled carbon monoxide or cotinine assays, potentially resulting in misclassification with respect to smoking category. However, since UPLIFT was not a smoking cessation study, it is unlikely that subjects would purposefully mislead the investigators as to their true smoking status. Fourth, the analyses reported herein are based on a post-hoc stratification of the subjects into smoking categories based on their smoking behavior not only at study entry but also during the course of the trial. Consequently, the validity of the p-values for assessing effects of treatment are not completely supported by randomization arguments, particularly given the imbalance between treatment groups within levels of post-hoc stratification that was observed at baseline. Instead of the stronger causality conclusions that could reasonably be inferred, the use of post-randomization defined subgroups implies that observed differences between randomization groups are associated with (and not necessarily caused by) differences in treatments. Finally, premature discontinuation was more likely to occur in those with more severe disease and preferentially occurred in the placebo group.[3] As a result, a healthy survivor effect occurs more frequently in the placebo group, which would bias the results against the active drug, tiotropium, and suggests

that the actual efficacy may be greater than that observed. The statistical approaches attempt to account for this problem are unlikely to fully adjust for the bias.

In summary, a subgroup analysis by smoking status was performed in 5,925 UPLIFT participants with available trial data who were classified as continuing smokers, intermittent smokers or continuing ex-smokers on the basis of their smoking behavior at both baseline and during the course of the trial. Continuing and intermittent smokers showed worse outcomes in terms of lung function decline than continuing ex-smokers and tiotropium had no discernible association with lung function decline in any smoking subgroup. On the other hand, tiotropium was associated with significant long-term benefits compared with placebo with respect to improvements in pre- and post-bronchodilator lung function irrespective of smoking status, reductions in the risk for and frequency of exacerbations across all smoking categories that was significant in the continuing ex-smokers, and statistically significant improvements in health-related quality of life in both continuing smokers and continuing ex-smokers. Tiotropium also was associated with a significant reduction in all-cause mortality in the continuing ex-smokers with a trend toward a mortality benefit in the intermittent smokers but not the continuing smokers. These observations should be considered in the setting of the trial in which patients were permitted to use other respiratory medications as prescribed by their physicians, except for inhaled anticholinergics, during the trial. These findings indicate that long-term treatment with tiotropium is associated with a beneficial impact on lung function and patient-reported outcomes across different smoking behaviors, although differences in the magnitude of benefit may occur. .

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Table 1. Baseline demographics of continuing smokers, intermittent smokers and continuing ex-smokers.

	Continuing Smokers			Intermittent Smokers			Continuing Ex-Smokers		
	Overall	Tiotropium	Placebo	Overall	Tiotropium	Placebo	Overall	Tiotropium	Placebo
Number of patients	846	414	432	1545	800	745	3534	1743	1791
% of total patients in trial	14.3	7.0	7.3	26.1	13.5	12.6	59.6	29.4	30.2
Percent male	66.5	71.5	61.8	73.3	74.9	71.5	77.1	76.4	77.7
Age (years)	60.7	60.9	60.5	62.3	62.4	62.2	66.4	66.3	66.4
GOLD Stage									
II	52.2	50.5	53.9	48.2	46.6	49.9	43.2	45.3	41.2
III	40.4	43.0	38.0	41.6	43.0	40.0	45.8	44.1	47.5
IV	6.4	5.8	6.9	8.3	8.3	8.5	9.3	9.1	9.5
Pre-bronchodilator									
FEV_1 (L)	1.19	1.20	1.19	1.13	1.12	1.15	1.06	1.07	1.05
FEV_1 % Predicted	41.2	41.0	41.4	39.9	39.6	40.3	38.8	39.1	38.4
FVC	2.72	2.74	2.70	2.67	2.66	2.69	2.59	2.58	2.59
SVC	2.83	2.87	2.80	2.83	2.82	2.84	2.78	2.78	2.78
Post-bronchodilator									
FEV_1 (L)	1.42	1.43	1.42	1.37	1.36	1.37	1.28	1.29	1.27
FEV_1 % Predicted	49.2	48.7	49.6	48.2	47.9	48.5	46.9	47.4	46.4
FVC	3.18	3.20	3.16	3.15	3.14	3.16	3.05	3.04	3.05
SVC	3.22	3.25	3.18	3.24	3.25	3.24	3.19	3.19	3.18
SGRQ	48.6	48.5	48.8	45.6	44.9	46.4	45.3	45.4	45.1

Table 2. Annualized rates of FEV_1 (mean ±SEM) change according to smoking status in the tiotropium and control groups.

Patient Characteristic	Tiotropium		Control		P-value
	n	FEV_1 rate (ml/yr)	n	FEV_1 rate (ml/yr)	
Pre-Bronchodilator FEV_1					
Continuing Smoker	313	-52 ± 4	303	-52 ± 4	0.99
Intermittent Smokers	758	-35 ± 2	672	-37 ± 2	0.64
Continuing Ex-smoker	1486	-23 ± 2	1438	-23 ± 2	0.85
Post-Bronchodilator FEV_1					
Continuing Smoker	312	-59 ± 4	305	-59 ± 4	0.98
Intermittent Smokers	758	-46 ± 2	673	-48 ± 3	0.57
Continuing Ex-smoker	1484	-33 ± 2	1432	-36 ± 2	0.19

Table 3. Mean (±SEM) pre and post-bronchodilator FEV_1 according to smoking status in the tiotropium and control groups

Patient Characteristic	Tiotropium		Control		Difference**
	n	FEV_1 (ml)	n	FEV_1 (ml)	
Pre-Bronchodilator FEV_1					
Day 1					
Continuing Smoker	308	1220 ± 20	301	1220 ± 20	
Intermittent Smokers	738	1130 ± 10	655	1160 ± 20	
Continuing Ex-smoker	1448	1090 ± 10	1407	1080 ± 10	
Month 1					
Continuing Smoker	305	1340 ± 10	298	1240 ± 10	100
Intermittent Smokers	735	1240 ± 10	649	1170 ± 10	70
Continuing Ex-smoker	1433	1190 ± 00	1390	1100 ± 00	90
Month 48					
Continuing Smoker	199	1160 ± 20	192	1040 ± 20	130
Intermittent Smokers	542	1110 ± 10	473	1050 ± 10	60
Continuing Ex-smoker	1036	1110 ± 10	915	1010 ± 10	100
Post-Bronchodilator FEV_1					
Day 1					
Continuing Smoker	312	1460 ± 20	303	1460 ± 30	
Intermittent Smokers	741	1360 ± 20	662	1390 ± 20	
Continuing Ex-smoker	1463	1310 ± 10	1409	1300 ± 10	
Month 1					
Continuing Smoker	309	1560 ± 10	302	1470 ± 10	90
Intermittent Smokers	733	1440 ± 10	653	1400 ± 10	40
Continuing Ex-smoker	1457	1380 ± 10	1400	1340 ± 10	40
Month 48					
Continuing Smoker	205	1330 ± 20	190	1240 ± 20	90
Intermittent Smokers	540	1270 ± 10	473	1240 ± 10	30*
Continuing Ex-smoker	1042	1260 ± 10	914	1210 ± 10	50

** $p<0.001$ for all differences (tiotropium – control) unless otherwise indicated
*$p=0.053$

Table 4. Exacerbation outcomes according to smoking status in the tiotropium and control groups

	Hazard Ratio (tiotropium/control) for Exacerbations		Number of Exacerbations per Patient-Year		Rate Ratio (tiotropium/control) for Number of Exacerbations per Patient-Year	
	Estimate	**95% CI**	**Control**	**Tiotropium**	**Estimate**	**95% CI**
			All exacerbations			
Continuing Smokers n = 846	0.80	0.67, 0.95	0.77	0.67	0.87	0.72, 1.04
Intermittent Smokers n = 1545	0.89	0.79, 1.00	0.76	0.69	0.90	0.80, 1.01
Continuing Ex-Smokers n = 3534	0.85	0.79, 0.92	0.83	0.69	0.83	0.77, 0.90
Exacerbation-Related Hospitalizations						
Continuing Smokers n = 846	0.91	0.68, 1.21	0.14	0.14	0.99	0.67, 1.46
Intermittent Smokers n = 1545	0.82	0.68, 0.99	0.17	0.14	0.87	0.68, 1.11
Continuing Ex-Smokers n = 3534	0.87	0.77, 0.99	0.16	0.16	0.97	0.82, 1.15

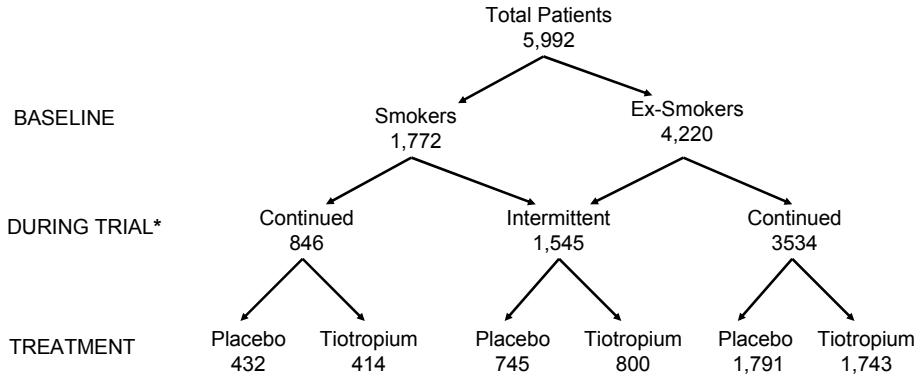
Table 5. Difference (tiotropium – control) in SGRQ domains at 6 and 48 months.

	6 months			48 months		
	N Tio, Control	Difference Mean (95% CI)	P value	N Tio, Control	Difference Mean (95% CI)	P value
Total Score						
Continuing Smokers	308, 297	-5.43 (−7.06, −3.80)	<0.0001	207, 189	-4.63 (−7.26, −2.00)	<0.001
Intermittent Smokers	717, 639	-2.09 (−3.29, −0.89)	0.0006	543, 459	-0.60 (−2.39, 1.19)	0.514
Continuing Ex-smokers	1428, 1375	-2.70 (−3.58, −1.83)	<0.0001	1037, 916	-2.74 (−3.99, −1.48)	<0.001
Impact Score						
Continuing Smokers	308, 297	-5.09(−7.00, −3.19)	<0.001	207, 189	-4.15 (−7.12, −1.17)	0.007
Intermittent Smokers	717, 639	-1.95(−3.33, −0.58)	0.0054	543, 459	-0.53 (−2.49, 1.44)	0.6
Continuing Ex-smokers	1428, 1375	-2.17(−3.15, −1.19)	<0.0001	1037, 916	-2.40 (−3.77, −1.03)	<0.001
Symptom Score						
Continuing Smokers	313, 301	-6.02 (−8.66, −3.38)	<0.0001	210, 192	-4.67(−8.40, −0.95)	0.014
Intermittent Smokers	739, 654	-2.72(−4.68, −0.77)	0.0064	555, 478	0.39 (−2.10, 2.88)	0.761
Continuing Ex-smokers	1449, 1405	-4.09(−5.46, −2.72)	<0.0001	1057, 933	-2.15(−3.94, −0.36)	0.019
Activity Score						
Continuing Smokers	308, 297	-6.17 (−8.31, −4.03)	<0.0001	207, 189	-5.69 (−8.67, −2.70)	<0.001
Intermittent Smokers	717, 639	-2.24 (−3.69, −0.80)	0.0024	543, 459	-1.49 (−3.63, 0.66)	0.173
Continuing Ex-smokers	1428, 1375	-2.71(−3.80, −1.63)	<0.0001	1037, 916	-3.46 (−4.96, −1.96)	<0.001

Table 6. Hazard ratio and associated 95% CI (tiotropium/placebo) for all cause mortality according to smoking behavior according to treatment group.

	Mortality Rate (%)	Hazard Ratio (tio/control)	95% CI
On-Treatment			
Continuing Smokers			
n = 846	16.4	1.2	0.85, 1.69
Intermittent Smokers			
n = 1545	10.0	0.87	0.63, 1.19
Continuing Ex-Smokers			
n = 3534	13.3	0.79	0.66, 0.95
Vital status (4-years)			
Continuing Smokers			
n = 846	18.4	1.24	0.90, 1.70
Intermittent Smokers			
n = 1545	11.2	0.85	0.63, 1.14
Continuing Ex-Smokers			
n = 3534	16.2	0.81	0.69, 0.96
Vital status (4-years + 30 days)			
Continuing Smokers			
n = 846	18.8	1.24	0.90, 1.70
Intermittent Smokers			
n = 1545	11.8	0.90	0.67, 1.20
Continuing Ex-Smokers			
n = 3534	16.4	0.83	0.71, 0.98

Figure 1. Patient numbers according to smoking status and treatment allocation.



*Smoking status known during trial (n=5,925)

Figure 2a. Pre-bronchodilator FEV_1 in the tiotropium and control group according to continuing smoking or continuing abstinence from smoking during 4 years.

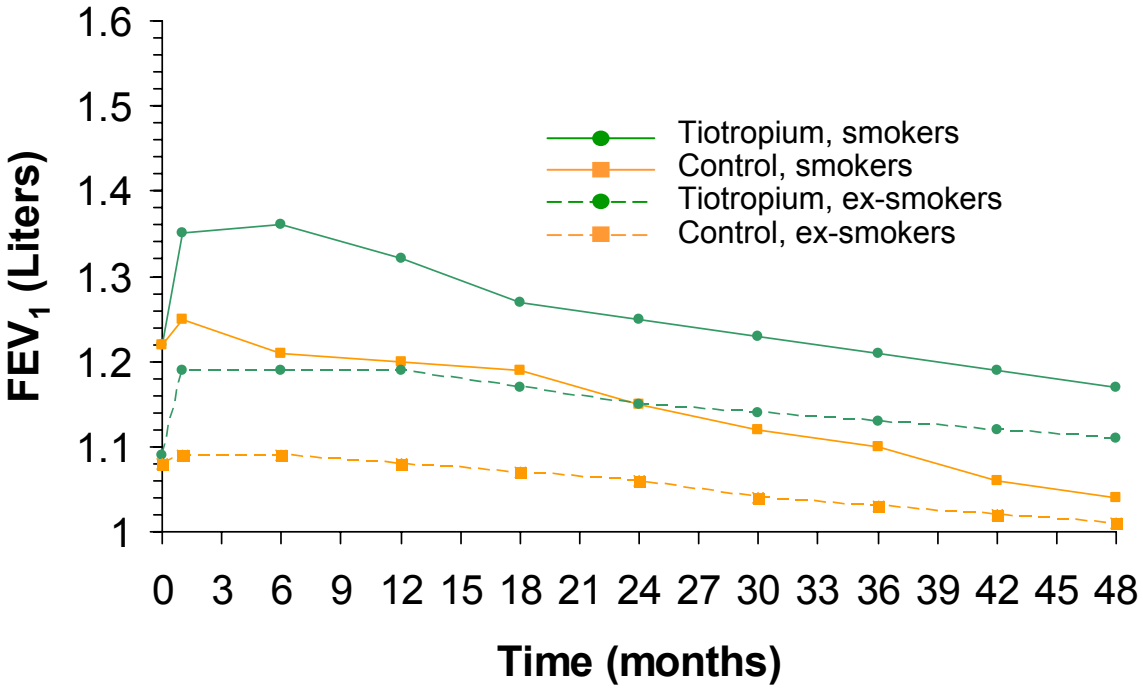


Figure 2b Post-bronchodilator FEV_1 in the tiotropium and control group according to continuing smoking or continuing abstinence from smoking during 4 years.

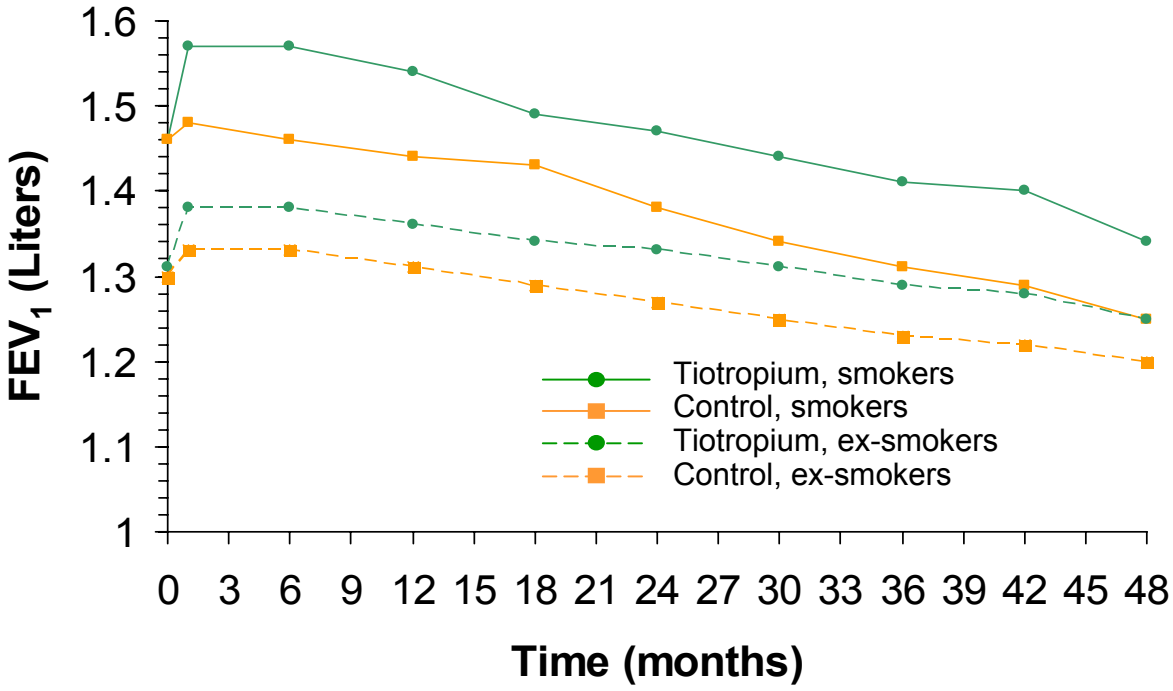


Figure 3a. Pre-bronchodilator FVC in the tiotropium and control group according to continuing smoking or continuing abstinence from smoking during 4 years.

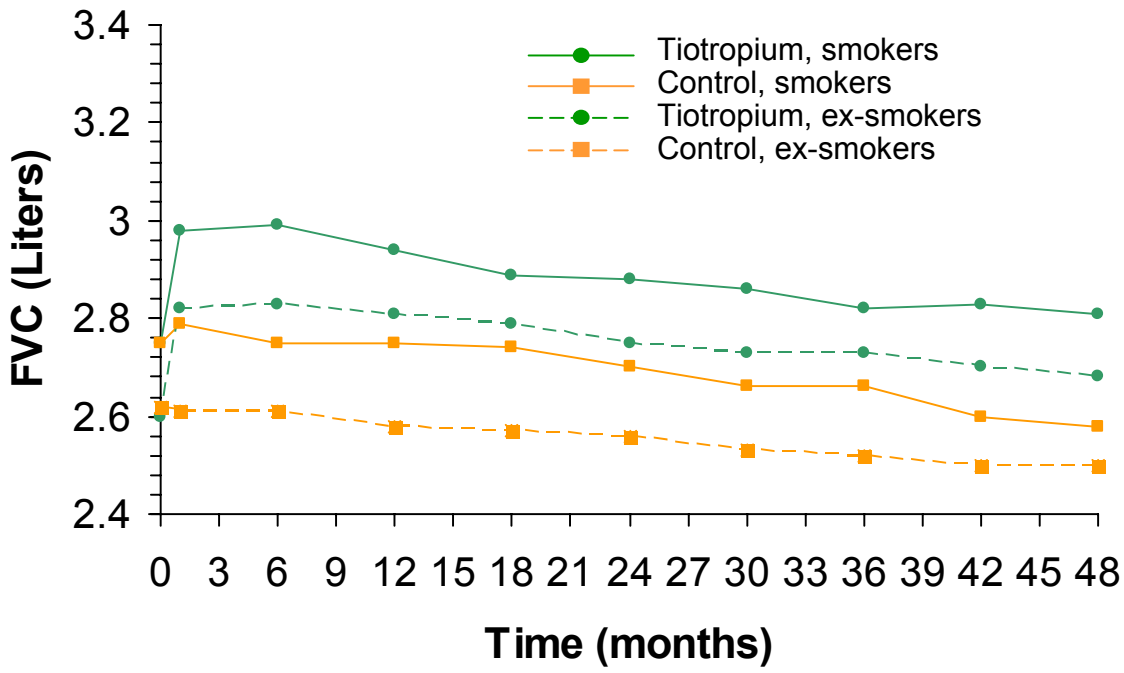
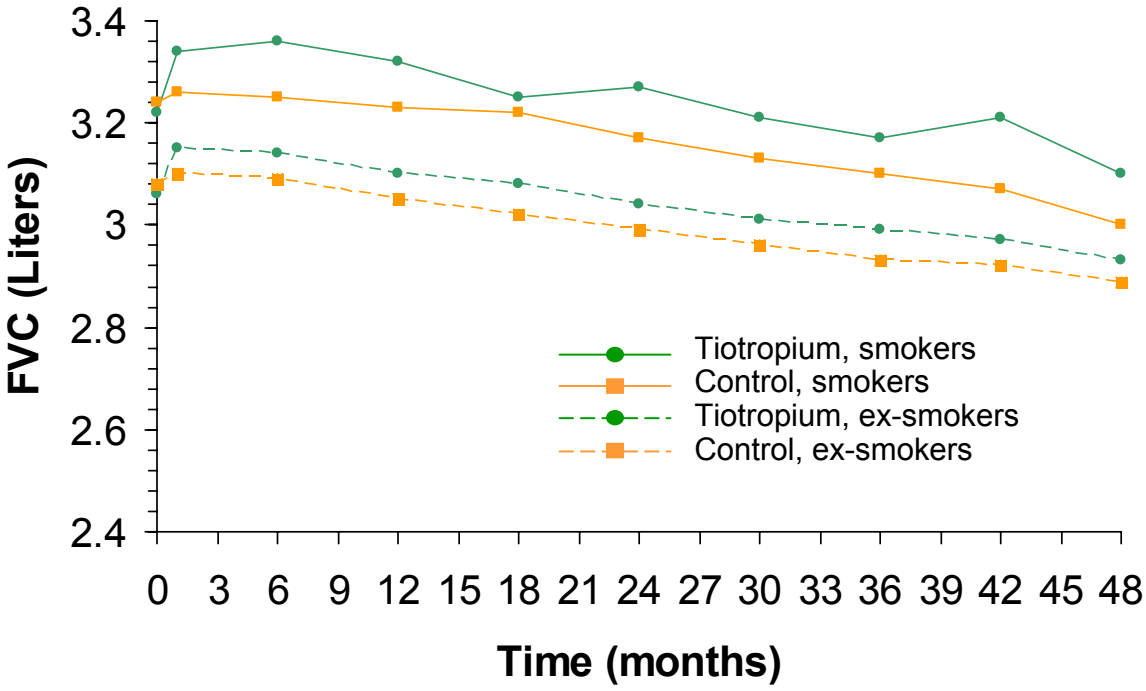


Figure 3b. Post-bronchodilator FVC in the tiotropium and control group according to continuing smoking or continuing abstinence from smoking during 4 years.



[Move Figure 4a. and 4b. to the online depository.]

Figure 4a. Pre-bronchodilator SVC in the tiotropium and control group according to continuing smoking or continuing abstinence from smoking during 4 years.

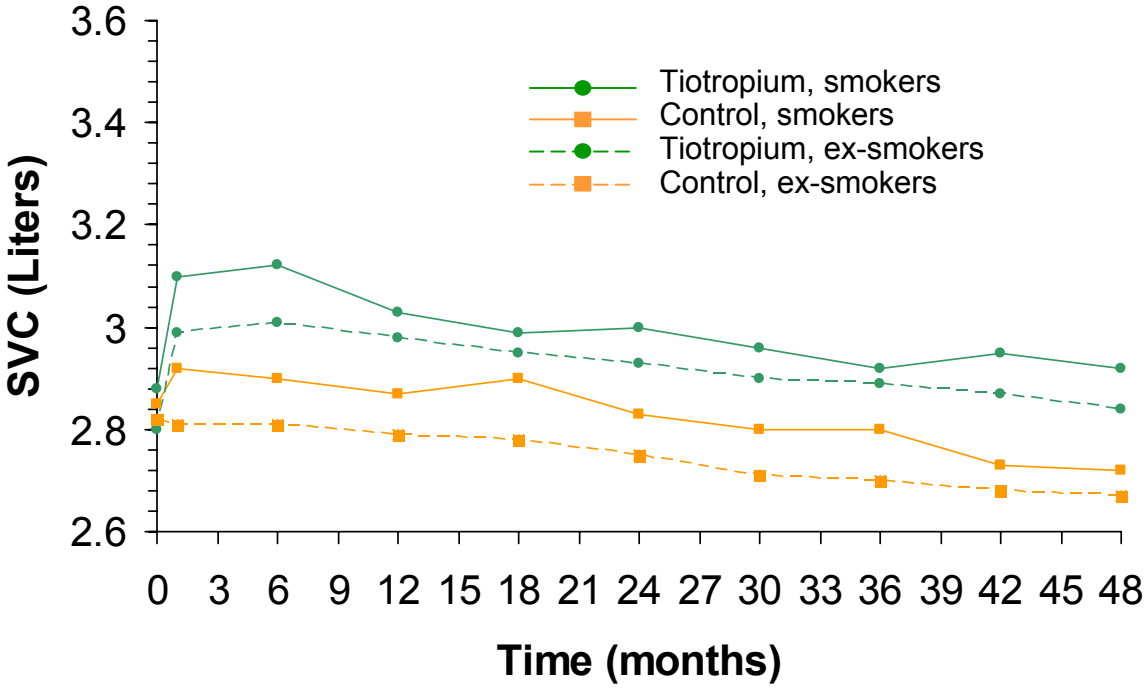


Figure 4b. Post-bronchodilator SVC in the tiotropium and control group according to continuing smoking or continuing abstinence from smoking during 4 years.