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COPD in young patients: A pre-specified analysis of the four-year trial of tiotropium (UPLIFT)

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Received 13 April 2010; accepted 26 July 2010

Available online 17 August 2010

KEYWORDS

Chronic obstructive pulmonary disease;
Tiotropium;
Age;
Lung function

Summary

Whilst recent large-scale studies have provided much evidence on the natural history and therapeutic response in patients with chronic obstructive pulmonary disease (COPD), relatively little is known about the effect in younger patients.

We report a pre-specified post-hoc analysis of 356 patients with COPD \leq 50 years old from the four year randomised, double blind placebo controlled Understanding Potential Long Term Impact on Function with Tiotropium (UPLIFT) trial. Inclusion criteria included a post-bronchodilator forced expiratory volume in 1 s (FEV_1) of \leq 70%, $FEV_1/FVC < 0.70$, age \geq 40 years, and smoking history of \geq 10 pack years.

Younger patients had a mean FEV_1 of 1.24 L (39% predicted) and an impaired health-related quality of life (St. George's Respiratory Questionnaire (SGRQ)) compared to the entire UPLIFT population. There were 40.2% women and 51.1% current smokers in the younger age group. Tiotropium was associated with a sustained improvement in spirometry and SGRQ. Mean decline in post-bronchodilator FEV_1 was 58 ml/year (placebo) vs. 38 ml/year (tiotropium) ($p = 0.01$). Corresponding values for pre-bronchodilator FEV_1 were 41 ml/year (placebo) compared with 34 ml/year (tiotropium) ($p = 0.34$). The hazard ratio (95%CI) for an exacerbation in the younger age group was 0.87(0.68, 1.13). The rate of exacerbations was reduced by tiotropium (rate ratio (95%CI) = 0.73(0.56, 0.95)).

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Tiotropium resulted in sustained bronchodilation, improved quality of life, and a decreased exacerbation rate in younger patients. Tiotropium also resulted in a significant reduction in the decline in post-bronchodilator FEV₁, suggesting possible disease modification by tiotropium in younger patients with COPD.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive debilitating disease which usually presents in later life with exertional dyspnoea. Partially reversible airflow obstruction as a consequence of long term tobacco smoking is the defining feature of the condition and the prevalence increases with increasing pack years.¹ A subgroup of smokers appears particularly vulnerable to the effects of tobacco smoke and develops COPD in their early years.² However, little is known of the natural history or response to therapy in these younger individuals.

There have been substantial improvements in the therapy of COPD with the introduction of long-acting beta agonists,³ long-acting anticholinergic drugs,⁴ and inhaled steroid/long acting beta agonist combination products.^{5,6} These agents have been demonstrated to improve a variety of physiologic and symptom parameters associated with the disease. Lung function, exercise duration and health-related quality of life are enhanced and exacerbation frequency decreased. Additionally, two recent large-scale studies have demonstrated a reduction of mortality approaching or above statistical and clinical significance.^{7,8} What has been harder to demonstrate is a significant effect on the progressive decline in lung function seen in COPD. Until recently the only intervention to demonstrate an impact on the rate of decline of lung function was smoking cessation.⁹ Publications based on the UPLIFT^{®10} and TORCH^{®7} studies have indicated the potential for pharmacotherapy to slow the decline in lung function in COPD. The demonstration of such potential disease modification with pharmacotherapy has important implications in the future management of the condition with respect to the utility of screening and early intervention.

Here we present a subgroup analysis of a pre-specified cohort of young patients from the UPLIFT trial who were ≤50 years of age on entry into the study. The objective of this analysis was to assess the 4-year progression of COPD and the effect of tiotropium in a subgroup of patients between the ages of 40 and 50 years who participated in the UPLIFT trial.

Methods

Study design

The study design and main results from the UPLIFT study have been reported elsewhere.¹¹ Briefly, UPLIFT was a randomised, double blind, parallel-group trial of once daily tiotropium in patients with spirometrically proven COPD older than or equal to 40 years of age. The post-bronchodilator FEV₁ was required to be 70% or less of the predicted value and

to be 70% or less than the FVC. A smoking history of greater than 10 pack years and a physician diagnosis of COPD were required for entry. The study was undertaken in 487 centres in 37 countries. The study was approved by the local ethical review boards of the participating centres and registered ([ClinicalTrials.gov:NCT00144339](http://ClinicalTrials.gov/NCT00144339)). Of note, in addition to the study medication, all patients could receive all prescribed respiratory medications, other than inhaled anticholinergics, throughout the trial.

The two treatment arms were tiotropium (18 mcg once daily) or matched placebo delivered via the HandiHaler inhalation device (Boehringer Ingelheim, Ingelheim, Germany). At the end of the four year study period (approximately day 1440) all patients were asked to stop the trial medication and were prescribed ipratropium two actuations (40 mcg) four times daily and asked to return for a further assessment 30 days later (approximately day 1470).

Following randomisation patients were seen at one month and three months with follow-up at three monthly intervals thereafter for four years. Spirometry (ATS criteria) was performed in accordance with strict quality control standards to obtain FEV₁, FVC and slow vital capacity (SVC). Every six months patients were asked to withhold their respiratory medication on the day of testing and pre-bronchodilator spirometry was performed. Study drug was then administered and patients given 80 mcg ipratropium followed 60 min later by 400 mcg salbutamol. Thirty minutes after salbutamol post-bronchodilator spirometry was performed. The yearly rates of decline in pre- and post-bronchodilator FEV₁ from day 30 until the completion of double blinded treatment were the co-primary endpoints. Secondary endpoints were three monthly lung functions, health-related quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ), exacerbations and exacerbations requiring hospital admission, and mortality from all causes. Mortality data was analyzed during the period from the first treatment day up until 30 days following the last dose of study medication ('on-treatment'), during the planned four years (1440 days) of study treatment and during the protocol defined period plus a 30 day washout period (1470 days). The latter two analyses included the vital status information of prematurely discontinued patients.

Statistical analysis

The co-primary endpoints and secondary endpoints of FVC, SVC and total score of SGRQ were analysed using random effects models. The decline of pulmonary function over time was analysed with random coefficient regression in which the pulmonary function value changed linearly after 30 days for each patient. The intercepts and slopes were random and the treatment effects were fixed. The mean effects at particular visits were estimated using repeated

measures analysis of covariance models, which did not require imputation of missing values. Time to first exacerbation and exacerbation-related hospitalisation was compared using Cox regression. The number of exacerbations and those leading to hospitalisation were estimated using Poisson regression, with adjustment for over dispersion and treatment exposure. None of the analyses have been adjusted for multiple comparisons.

Results

Patient characteristics

Of the 5993 patients randomised in UPLIFT, 356 were aged 50 years or younger. The flow of patients into the study is described in the CONSORT diagram (Fig. 1). The baseline characteristics of these younger patients and those aged over 50 years of age are listed in Table 1. There were a greater number of women in the ≤ 50 years group but the severity of disease as classified by GOLD stage was similar to the total population. Approximately half of the patients were in GOLD stage II. Conversely, despite the relatively young age of this subpopulation, nearly 50% had severe or very severe disease with an average FEV₁ percent predicted that was comparable to that in the older age groups. Approximately half of the ≤ 50 years cohort continued to smoke, whereas there was a progressive decrease in the percentage of continuing smokers with age. Despite having similar objective indices of disease

severity, health-related quality of life was substantially poorer in the patients under 50 years, as reflected in the higher SGRQ score.

Use of concomitant medication in the younger age group was high and similar to the total study population. Approximately 50% of the younger patients were taking inhaled corticosteroids and long acting beta agonists either in a combination inhaler or as separate inhalers.

A total of 65 patients (38%) from the placebo group and 51 (28%) from the tiotropium group prematurely discontinued trial medication. More patients discontinued from the placebo group compared to the tiotropium group due to adverse events (21 vs. 13 patients) and because of worsening COPD (11 vs. 4 patients).

Lung function outcome

The co-primary endpoints of rate of decline in pre and post-bronchodilator FEV₁ tended to be improved by tiotropium. In the case of post-bronchodilator change in FEV₁ this was statistically significant at 58 ml/year vs. 38 ml/year; $p = 0.01$ (Table 2). This improvement in the rate of FEV₁ decline appeared consistent across the treated population and no association with possible confounding variables was seen. The between group difference in the decline in pre-bronchodilator FEV₁ was 7 ml/year ($p = 0.34$). The significant improvement in rate of decline in post-bronchodilator FEV₁ in patients ≤ 50 years is in contrast to the findings in the total UPLIFT population. In the whole study population annual decline in FEV₁ was similar in both tiotropium and

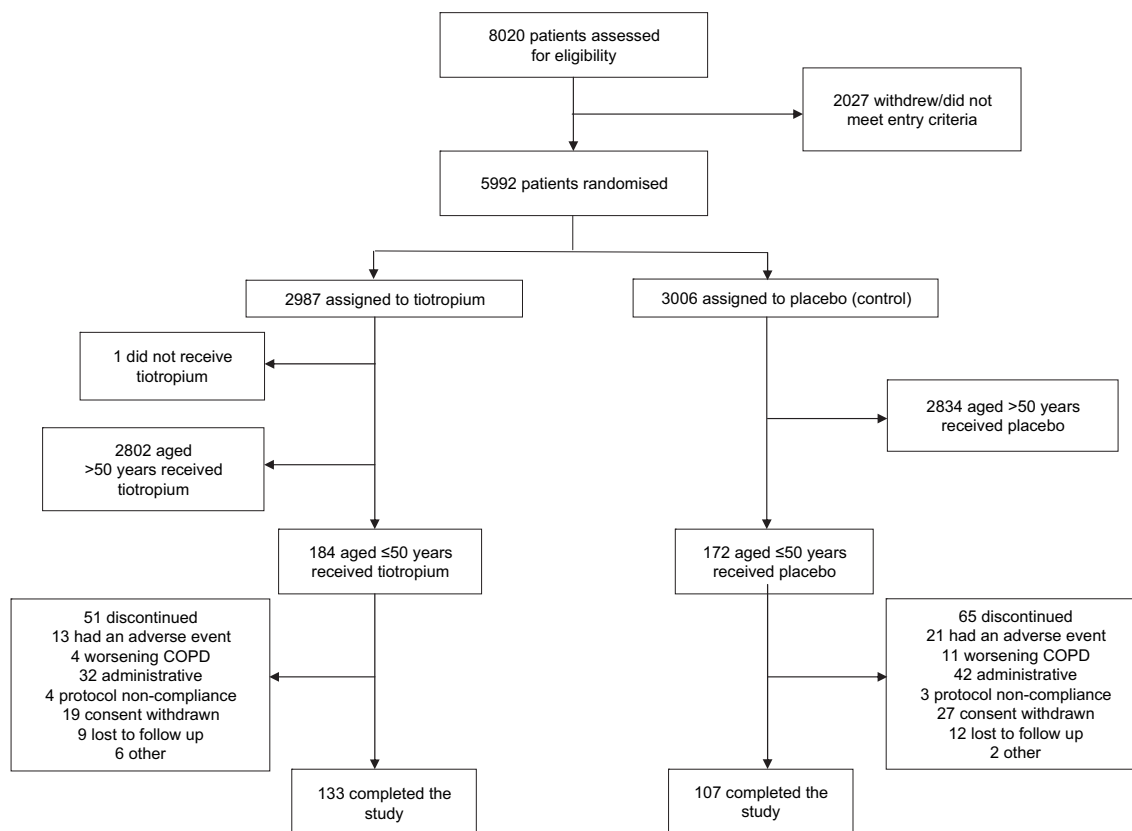


Figure 1 A CONSORT diagram describing the flow of study patients.

Table 1 Baseline demographics of the tiotropium and control groups according to age.

	≤50 years		50–60 years	60–70 years	>70 years	
	Tiotropium (n = 184)	Control (n = 172)	Total (n = 356)	Total (n = 1563)	Total (n = 2511)	Total (n = 1562)
Male, %	61.4	58.1	59.8	70.0	75.8	80.9
Mean GOLD stage, %						
II	50.5	47.7	49.2	46.4	45.0	45.3
III	37.0	35.5	36.2	41.5	44.9	46.7
IV	11.4	15.1	13.2	11.0	8.1	6.3
Smoking history, %						
Ex-smoker	54.3	43.0	48.9	57.6	72.2	85.3
Current smoker	45.7	57.0	51.1	42.4	27.8	14.7
Mean COPD duration, yrs (SD)	7.1 (5.6)	7.8 (6.3)	7.4 (5.9)	8.8 (6.3)	10.1 (7.5)	10.8 (8.5)
Respiratory medication, %						
LABA	55.4	59.3	57.3	58.5	60.5	61.8
ICS	56.0	60.5	58.1	60.3	61.9	63.8
Combination ICS + LABA	45.1	47.7	46.3	48.2	48.7	50.1
Anticholinergic	39.1	35.5	37.4	42.9	46.0	48.6
Mean pre-bronchodilator (SD)						
FEV ₁ (L)	1.28 (0.47)	1.20 (0.46)	1.24 (0.47)	1.18 (0.44)	1.09 (0.38)	0.99 (0.34)
FEV ₁ (% predicted)	39.6 (12.8)	38.5 (13.4)	39.1 (13.1)	39.1 (12.6)	39.4 (11.8)	39.8 (11.3)
FVC (L)	2.85 (0.84)	2.78 (0.92)	2.82 (0.87)	2.80 (0.85)	2.60 (0.80)	2.44 (0.75)
SVC (L)	2.99 (0.85)	2.93 (0.85)	2.96 (0.85)	2.95 (0.86)	2.79 (0.82)	2.62 (0.75)
Mean post-bronchodilator (SD)						
FEV ₁ (L)	1.55 (0.52)	1.48 (0.53)	1.51 (0.52)	1.42 (0.48)	1.31 (0.42)	1.19 (0.37)
FEV ₁ (% predicted)	48.1 (13.9)	47.3 (15.0)	47.7 (14.4)	47.1 (13.3)	47.6 (12.4)	47.9 (12.0)
FVC (L)	3.32 (0.89)	3.27 (0.97)	3.30 (0.93)	3.28 (0.90)	3.09 (0.88)	2.86 (0.81)
SVC (L)	3.40 (0.89)	3.29 (0.93)	3.35 (0.91)	3.36 (0.92)	3.21 (0.89)	3.00 (0.81)
Mean SGRQ Total Score (SD)	48.2 (18.6)	48.2 (18.0)	48.2 (18.3)	48.0 (17.5)	44.9 (16.9)	44.8(16.6)

GOLD, Global Initiative for Chronic Obstructive Lung Disease; LABA, long-acting β -agonists; ICS, inhaled corticosteroids; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; SVC, slow vital capacity; SGRQ, St George's Respiratory Questionnaire.

placebo groups at 30 ml/year before bronchodilation and 40 ml/year (tiotropium) and 42 ml/year (control) after bronchodilation. There was no significant difference in the rate of decline of FVC or SVC in patients ≤50 years when tiotropium was compared with controls.

There were sustained improvements in lung function throughout the trial associated with tiotropium (Fig. 2a and b). Both pre and post-bronchodilator FEV₁ were significantly greater in the tiotropium group than the control group at all time points ($p < 0.05$). The differences ranged from 82 to 148 ml and 58–172 ml, respectively. Pre-bronchodilator FVC improvements in the tiotropium group were significantly greater than the control at all time points ($p < 0.05$) except for month 18. Post-bronchodilator FVC measurements were greater in the

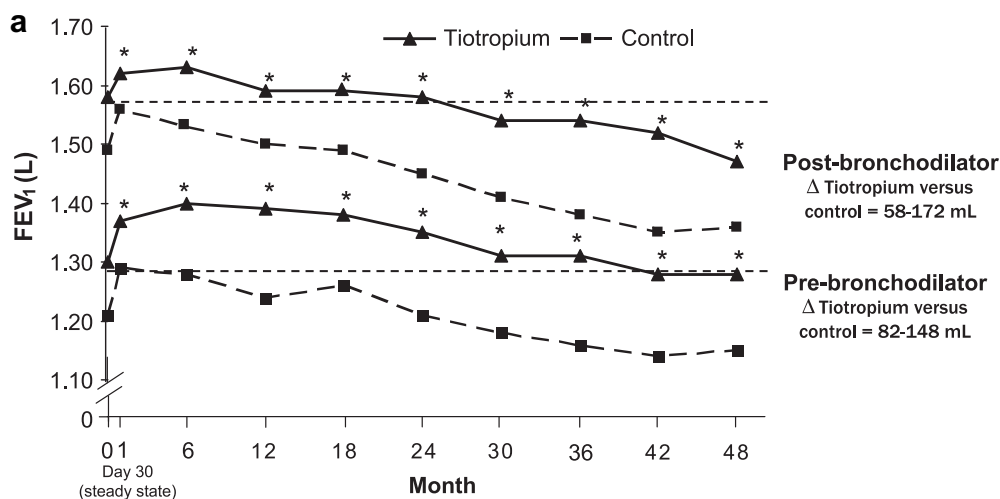
tiotropium group and this achieved statistical significance for months 36 and 42.

Health-related quality of life

Tiotropium was associated with improvements in the SGRQ total score throughout the study period (Fig. 3) with this improvement being statistically significant at half of the clinic visits. The mean differences (tiotropium – control) were –3.3, –3.0 and –4.1 units at 1, 2 and 3 years in favour of tiotropium. The mean difference was –3.9 at 42 months and fell to +0.9 units at 48 months. However at 48 months, SGRQ total score data were not available for 41.9% of patients in the placebo group and 34.2% of patients in the tiotropium group.

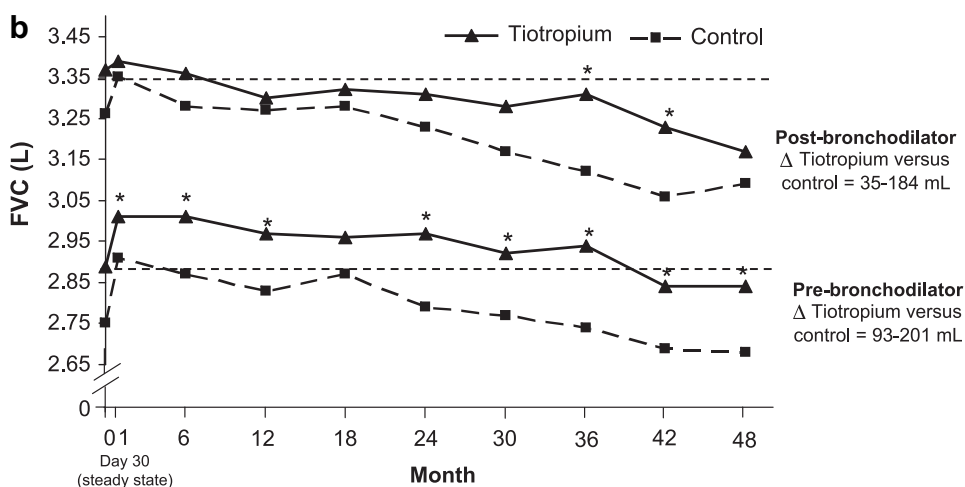
Table 2 Mean (SE) rate of decline (ml/yr) in pre-bronchodilator and post-bronchodilator FEV₁ in the tiotropium and control patients ≤50 years old.

	Tiotropium	Control	Difference	<i>p</i> -value
Pre-bronchodilator FEV ₁	34 (5)	41 (5)	7 (7)	0.34
Post-bronchodilator FEV ₁	38 (5)	58 (6)	19 (8)	0.01
Pre-bronchodilator FVC	49 (11)	55 (11)	6 (5)	0.69
Post-bronchodilator FVC	52 (10)	69 (11)	17 (15)	0.26



FEV₁, forced expiratory volume in 1 second

* $p < 0.05$ versus control. Repeated measure analysis of variance was used to estimate means. Estimated means are adjusted for baseline measurements. Patients with ≥ 3 measurements after Day 30 were included in the analysis.



FVC, forced vital capacity

* $p < 0.05$ versus control. Repeated measure analysis of variance was used to estimate means. Estimated means are adjusted for baseline measurements. Patients with ≥ 3 measurements after Day 30 were included in the analysis.

Figure 2 Estimated mean pre and post-bronchodilator FEV₁ (a) and FVC (b) throughout the UPLIFT trial in the tiotropium and control groups in patients ≤ 50 years of age.

Exacerbations

The rate of exacerbations was significantly diminished by treatment with tiotropium (Table 3) with a rate ratio of 0.73 ($p = 0.02$). The hazard ratio (tiotropium/control) for the first exacerbation was 0.87 ($p = 0.30$). Hospitalisations were infrequent in this population and there was no significant difference between treatment arms.

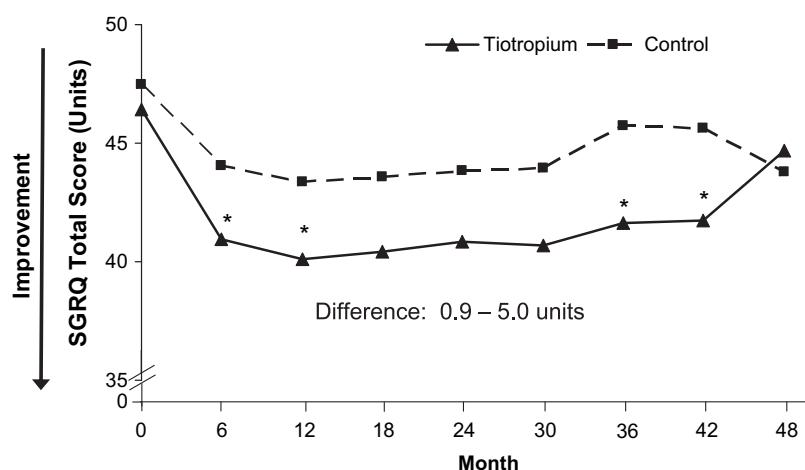
Mortality

Mortality was relatively low in patients ≤ 50 years of age, namely $\leq 7\%$ for both treatment groups. Tiotropium was associated with a lower mortality rate (Fig. 4) but this did not reach statistical significance. For the protocol-defined intention-to-treat period (including vital status information

until day 1440), the hazard ratio (95% CI) for tiotropium/control was 0.77 (0.33, 1.79) and was based on 10 deaths in the tiotropium group and 12 in the placebo group. The most common cause of death was an exacerbation of COPD (tiotropium 4, placebo 5). A specific cause of death could not be determined in 4 cases (tiotropium 1, placebo 3). No other events occurred in more than 2 patients in either treatment group.

Interactions by age

Although tests for treatment interaction by age were conducted, the interpretation is limited by either the sample sizes within an age subgroup or the infrequency of an event (i.e. fatal events). However, there was a significant interaction by age for pre-bronchodilator FEV₁ (until month 36)



SGRQ, St George's Respiratory Questionnaire
 * $p < 0.05$ vs. control. Repeated measure ANOVA was used to estimate means. Estimated means are adjusted for baseline measurements. Patients with ≥ 2 acceptable SGRQ Total Scores after Month 6 were included in the analysis.

Figure 3 Estimated mean St. George's Respiratory Questionnaire total score throughout the UPLIFT trial in the tiotropium and control groups in patients ≤ 50 years of age.

and for pre-bronchodilator FVC (throughout the trial), which could be suggestive of a difference in the magnitude of treatment benefit across age groups.

Discussion

The UPLIFT trial was a 4-year randomized, double-blind trial involving 5992 patients who received tiotropium HandiHaler[®] 18 mcg daily for up to 4 years. The size and the duration of the trial along with the inclusion and exclusion criteria resulted in a broad selection of patients, which is conducive to examination of subgroups that might be of particular medical and scientific interest. One such population comprises patients who would be considered as being relatively young for the development of moderate to very severe COPD. A total of 356 patients ≤ 50 years of age were identified. Treatment with tiotropium resulted in a significant slowing of the annualized rate of decline in post-bronchodilator, but not pre-bronchodilator FEV₁ along with sustained improvements in lung function relative to placebo throughout 4 years. As well, a reduced rate of exacerbations and improvements in health-related quality of life were observed, although not all exacerbation variables and SGRQ differences achieved nominal statistical significance.

The major novel finding of this subgroup analysis is the significant effect of tiotropium on one of the co-primary endpoints, rate of decline in post-bronchodilator FEV₁. The magnitude of the reduction in the rate of decline of FEV₁ over time with tiotropium appears larger for the post-bronchodilator value compared to the pre-bronchodilator value. It is possible that the post-bronchodilator FEV₁ is a more stable value in that essentially all influence of bronchomotor tone has been removed (i.e. salbutamol 4 actuations + ipratropium 4 actuations sequentially administered to achieve peak effects of both). The pre-bronchodilator value theoretically remains subject to circadian variation and the potential external influences on smooth muscle tone. The effects of this may be more prominent over time given that the disease is progressive (i.e. a given degree of smooth muscle tone on the radius will be inversely proportional to the 4th power of the radius).

A similar outcome has recently been reported in the UPLIFT subpopulation with GOLD stage II disease.¹⁰ Whilst some of the patients reported in the latter subgroup analysis are also included in this current analysis, they represent only half of the population studied. That similar findings have been revealed by two sub-analyses suggests a potentially disease modifying effect of long-term tiotropium, and provides great impetus for the early detection

Table 3 Exacerbation outcomes in the tiotropium and control patients ≤ 50 years old.

	Tiotropium (<i>n</i> = 184)	Control (<i>n</i> = 172)	Ratio (tiotropium/control) (95% CI)	<i>p</i> -value
Number of exacerbations/patient year, mean (95% CI) ^a	0.59 (0.49, 0.72)	0.81 (0.68, 0.97)	RR 0.73 (0.56, 0.95)	0.02
Time to first exacerbation, median months (95% CI) ^b	16.4 (11.3, 20.1)	10.5 (6.9, 17.6)	HR 0.87 (0.68, 1.13)	0.30
Number of hospitalizations for exacerbation/ patient year, mean (95% CI) ^a	0.13 (0.09, 0.19)	0.14 (0.09, 0.21)	RR 0.93 (0.52, 1.67)	0.82

CI, confidence interval; RR, rate ratio; HR, hazard ratio.

^a Estimated using Poisson regression with Pearson over dispersion model adjusting for time at risk.

^b Calculated using Cox regression.

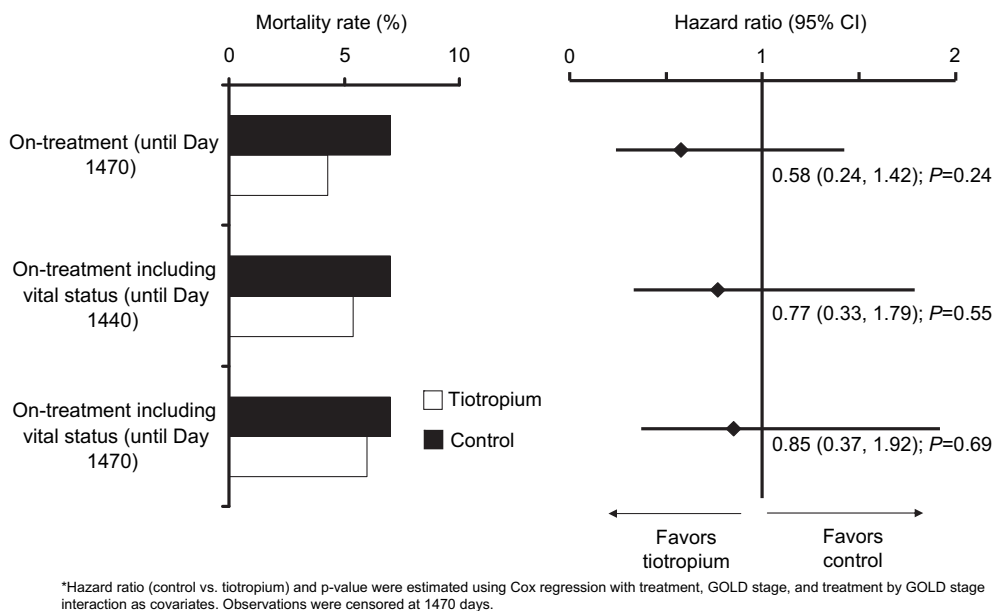


Figure 4 Mortality rates and hazard ratios (tiotropium/control) in patients ≤ 50 years of age.

and treatment of this condition. Several small scale surveys looking at the rate of detection of COPD in primary care settings worldwide demonstrate that many patients with early stage disease remain undetected and under-treated.^{12–14} If the object of treatment is purely symptomatic relief then this may be considered acceptable. However, if disease progression can be halted then community surveillance in younger patients and those with milder disease becomes imperative.

In both GOLD stage II and in patients ≤ 50 years of age in UPLIFT, the post-bronchodilator decline in FEV₁ was significantly diminished by tiotropium therapy. In contrast whilst the pre-bronchodilator FEV₁ decline was numerically less in the tiotropium than the placebo group this difference did not achieve statistical significance. It is likely that there are several disease processes at play in the pathology of COPD, including mucus hypersecretion, parenchymal destruction and an increase in cholinergic tone, chronic inflammation in small airways with fibrotic thickening and the effect of exacerbations.^{15–17} The differential expression of these pathological processes may explain the different phenotypes, such as emphysema and chronic bronchitis, seen within COPD. It appears from the longitudinal spirometric observations that tiotropium may influence COPD in a disease modifying fashion, an effect which is revealed by the removal of airways tone following bronchodilation. The administration of study drug, 80 mcg ipratropium and 400 mcg salbutamol at appropriate timings will induce full relaxation of the airway minimising any tonic bronchospasm. Airflow limitation will then reflect non-muscular airway collapse, secondary to the loss of the parenchymal scaffold, mucus plugging and airway wall thickening. The slower decline in post-bronchodilator FEV₁ with tiotropium may, because of sustained bronchodilation and reduction in airway collapse, lessen airway inflammation and consequently decrease lung destruction. Pre-bronchodilator FEV₁ changes may be masked by the relative impact of, and the diurnal variability in, the increased airway tone which characterises COPD.

This subgroup analysis of patients 50 years or younger from the UPLIFT trial dataset confirms that the previously demonstrated benefits seen in the whole study population also apply to younger patients. Treatment with tiotropium is associated with a sustained bronchodilation with values only returning to pre-study baseline towards the end of the four year study period. The degree of bronchodilation seen was similar to that observed in the whole UPLIFT population when compared to placebo (increase in pre-bronchodilator FEV₁ ranged from 87 to 103 ml throughout the trial for the entire population).

Tiotropium improved SGRQ and reduced exacerbations during the UPLIFT study in patients ≤ 50 years of age. The size of the effect for the SGRQ total score, however, was at the borderline of the reported minimal clinically importance difference of 4 units. The high baseline SGRQ indicates that the quality of life of these younger patients with COPD was significantly impacted by their disease. The lack of difference between placebo and tiotropium treatment seen at 48 months may reflect the considerably fewer numbers of patients from whom data was obtained at this time point for this particular assessment of SGRQ and possible effects from preferential discontinuation of more severely afflicted patients in the control group. Regarding exacerbations, there was a lower rate in the patients ≤ 50 years than in the whole UPLIFT population (0.59 (tiotropium) vs. 0.81 (placebo) per patient year), but the reduction associated with tiotropium therapy is consistent with that seen in the whole study population. The hazard ratio for time to first exacerbation indicated a reduction in risk, although the confidence interval included 1, which likely reflects the smaller sample size of the subgroup (and corresponding loss of precision of the estimate).

Evaluation of baseline characteristics revealed the presence of significant COPD in younger patients. When baseline spirometry is taken as percent predicted then there is a remarkable similarity of the FEV₁ in each decade

in the UPLIFT population. Mean FEV₁ varies between 38 and 40% of predicted. An obvious hypothesis to explain the early onset of COPD in the younger patient is that they have worse disease with an increased rate of deterioration to severe airflow obstruction at an earlier age. The observed rate of decline of pre-bronchodilator FEV₁ in the placebo treated group is 30 ml/year in the total UPLIFT population compared to 41 ml/year in our younger population. The latter slope approximates to the rate of decline needed to achieve the degree of baseline airflow obstruction seen here, provided that the disease started when the patient took up smoking. Older patients with a slower rate of lung function decline may therefore have a delay in the onset of moderate to severe airflow obstruction; alternatively, their lung function may have started to decline at an accelerated rate at an older age. Younger patients had fewer pack years (mean 33 years) compared to the 45 pack years of the older cohort, but being chronologically younger they will have had greater annual tobacco consumption. Another possible explanation is a natural selection of individuals with a slower rate of decline based on the interaction of genetics and environment permitting prolonged survival with COPD.

As stated, these younger patients had a similar disease profile in terms of FEV₁ % predicted and GOLD staging compared to the whole UPLIFT population. Despite this similarity, patients reported at baseline a lower (i.e. worse) health-related quality of life than older patients. It is possible that this greater impairment is due to the greater impact of the symptoms of COPD in a normally more active, younger population. The population of younger patients in the UPLIFT study, with early onset of disease and a rapid lung function decline, might represent a unique phenotype and possibly genotype.

Women comprised 40% of the patients ≤50 years in UPLIFT. This may represent an increase in the proportion of younger women smoking in the general population and is reflected by a worldwide increase in women with COPD, as well as hospitalisations and deaths due to COPD.^{18,19} Whether there are important sex-related differences in the development or progression of COPD or in response to treatment has been much debated. The difference in the number of women in the younger subgroup compared to that in the older age groups is relatively small, however, and would not be expected to influence the findings of this analysis.

In the entire UPLIFT population there is a progressive decrease in the percentage of active smokers with increasing age. Over half of the patients aged <50 reported continued smoking compared with less than 15% of patients aged over 70 years. There could be several explanations for this observation. First, smoking cessation frequently requires multiple attempts before successful quitting is achieved.²⁰ Older patients will therefore have a longer time to undertake serial efforts. Continued smoking not only increases the decline in lung function with COPD but also puts the smoker at risk of many other smoking-related disorders. It is possible that a high rate of attrition from other smoking-related diseases is responsible for a progressive loss of smokers from the age profile. It is interesting to note that continued smoking appeared to counterbalance the beneficial effect of tiotropium on mortality seen in the whole UPLIFT population.²¹ In

contrast to the similar GOLD staging and lower quality of life seen in the patients aged 50 years and younger, absolute baseline spirometric values were higher than for the rest of the study population. Thus, this population illustrates the marked age dependency of the metrics used in our assessment of COPD. We also acknowledge that the upper limit of FEV₁ for inclusion was 70% predicted and further data should be generated in younger patients with milder disease.

As with any subgroup analysis, even if pre-specified, there are a number of limitations inherent in this methodology. Since patients were recruited from pulmonary specialty practices it is likely that the patient population studied does not reflect that seen in primary care. The ten year follow-up of the European Community Respiratory Health Survey demonstrates that 6% of younger people have spirometry values below that required to achieve GOLD stage II COPD.² Symptomatic patients had a greater rate of decline in lung function than those who were asymptomatic.²² Similarly, the population reported here was required to have physician diagnosed COPD and therefore likely reflects symptomatic patients who sought medical attention rather than those with merely reduced spirometry perhaps identified through screening.

This analysis of patients ≤50 years who took part in the UPLIFT study has demonstrated improvements in lung function, quality of life and exacerbation frequency with tiotropium treatment, indicating the benefits of maintenance pharmacotherapy in younger patients with COPD. Furthermore, the reduction in the decline in post-bronchodilator FEV₁ with tiotropium suggests that, in addition to providing symptomatic benefits and reduced rate of exacerbations, continued treatment may reduce disease progression. The analysis presented provides a justification and rationale for early diagnosis and treatment in young patients with COPD.

Author's role: All of the authors have made substantial contributions to 1) the conception and design of the study or acquisition of data or analysis and interpretation of data, 2) drafting the article or revising it critically for important intellectual content and 3) final approval of the version to be submitted.

Conflicts of interest

AM has received consulting fees from Boehringer Ingelheim, Pfizer, GlaxoSmithKline, and Proctor & Gamble, lecture fees from Boehringer Ingelheim and AstraZeneca, and grant support from Proctor & Gamble. BC has received consulting fees from Almirall, AstraZeneca, Boehringer Ingelheim, and GlaxoSmithKline, lecture fees from Almirall, AstraZeneca, Boehringer Ingelheim, Forrest, and GlaxoSmithKline, and grant support from Boehringer Ingelheim, Forrest, and GlaxoSmithKline. SK and TL are employees of Boehringer Ingelheim. TL has stock ownership in Affymetrix, Amgen, AstraZeneca, Medco Health Solutions, Merck, and Oncogenex Pharmaceuticals. DT has received consulting fees from AstraZeneca, Boehringer Ingelheim, Dye Laboratories and Shering, lectures fees from AstraZeneca, Boehringer Ingelheim, and Dye Laboratories, and grant support from Almirall, AstraZeneca, Boehringer Ingelheim, Dey Laboratories,

GlaxoSmithKline, Ivax, MediciNova, Nabi Biopharmaceuticals, Novartis, Pfi zer, and Sepracor. MD has received consulting fees from Boehringer Ingelheim, Pfizer, GlaxoSmithKline, and Nycomed, lecture fees from Boehringer Ingelheim and Pfizer, and grant support from AstraZeneca.

References

- Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. *Lancet* 2007;**370**:765–73.
- de Marco R, Accordini S, Cerveri I, Corsico A, Sunyer J, Neukirch F, Kunzli N, Leynaert B, Janson C, Gislason T, Vermeire P, Svanes C, Anto JM, Burney P. An international survey of chronic obstructive pulmonary disease in young adults according to GOLD stages. *Thorax* 2004;**59**:120–5.
- Boyd G, Morice AH, Pounsford JC, Siebert M, Pelsis N, Crawford C. An evaluation of salmeterol in the treatment of chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1997;**10**:815–21.
- Casaburi R, Mahler DA, Jones PW, Wanner A, San PG, ZuWallack RL, Menjoge SS, Serby CW, Witek Jr T. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002;**19**:217–24.
- Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, Anderson J, Maden C. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003;**361**:449–56.
- Szafranski W, Cukier A, Ramirez A, Menga G, Sansores R, Nahabedian S, Peterson S, Olsson H. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. *Eur Respir J* 2003;**21**:74–81.
- Celli BR, Thomas NE, Anderson JA, Ferguson GT, Jenkins CR, Jones PW, Vestbo J, Knobil K, Yates JC, Calverley PM. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. *Am J Respir Crit Care Med* 2008;**178**:332–8.
- Celli B, Decramer M, Kesten S, Liu D, Mehra S, Tashkin DP. Mortality in the 4-year trial of tiotropium (UPLIFT) in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009;**180**:948–55.
- Kerstjens HA, Brand PL, Postma DS. Risk factors for accelerated decline among patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;**154**:S266–72.
- Decramer M, Celli B, Kesten S, Lystig T, Mehra S, Tashkin DP. Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. *Lancet* 2009;**374**:1171–8.
- Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, Decramer M. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;**359**:1543–54.
- Bednarek M, Maciejewski J, Wozniak M, Kuca P, Zielinski J. Prevalence, severity and underdiagnosis of COPD in the primary care setting. *Thorax* 2008;**63**:402–7.
- Takahashi T, Ichinose M, Inoue H, Shirato K, Hattori T, Takishima T. Underdiagnosis and undertreatment of COPD in primary care settings. *Respirology* 2003;**8**:504–8.
- Buffels J, Degryse J, Heyrman J, Decramer M. Office spirometry significantly improves early detection of COPD in general practice: the DIDASCO Study. *Chest* 2004;**125**:1394–9.
- Chung KF, Adcock IM. Multifaceted mechanisms in COPD: inflammation, immunity, and tissue repair and destruction. *Eur Respir J* 2008;**31**:1334–56.
- Bathoorn E, Kerstjens H, Postma D, Timens W, MacNee W. Airways inflammation and treatment during acute exacerbations of COPD. *Int J Chron Obstruct Pulmon Dis* 2008;**3**:217–29.
- Hogg JC, Timens W. The pathology of chronic obstructive pulmonary disease. *Annu Rev Pathol* 2009;**4**:435–59.
- Mannino DM. Women and chronic obstructive pulmonary disease: does sex influence survival? *Am J Respir Crit Care Med* 2006;**174**:488–9.
- Mannino DM, Reichert MM, Davis KJ. Lung function decline and outcomes in an adult population. *Am J Respir Crit Care Med* 2006;**173**:985–90.
- Furberg H, Sullivan PF, Maes H, Prescott CA, Lerman C, Bulik C, Kendler KS. The types of regular cigarette smokers: a latent class analysis. *Nicotine Tob Res* 2005;**7**:351–60.
- Tashkin DP, Celli B, Kesten S, Lystig T, Mehra S, Decramer M. Long-term efficacy of tiotropium in relation to smoking status in the UPLIFT trial. *Eur Respir J*; 2009.
- de Marco R, Accordini S, Anto JM, Gislason T, Heinrich J, Janson C, Jarvis D, Kunzli N, Leynaert B, Marcon A, Sunyer J, Svanes C, Wjst M, Burney P. Long-term outcomes in mild/moderate chronic obstructive pulmonary disease in the European community respiratory health survey. *Am J Respir Crit Care Med* 2009;**180**:956–63.