ERJ Express. Published on February 25, 2010 as doi: 10.1183/09031936.00127809

Tiotropium as a First Maintenance Drug in COPD: Secondary Analysis of the UPLIFT trial.

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Word Count: Abstract 196/ Full text Body 4227

Source of Financial support and Role of Authors / Sponsor

This study was funded by Boehringer Ingelheim and Pfizer. The design of the trial, monitoring of the trial conduct, approval of the statistical analysis, review of the data, and writing of the manuscript involved a joint advisory committee including D. Tashkin, B. Celli, M. Decramer, and S. Kesten. T. Troosters reviewed the data and participated in writing of the manuscript. S. Mehra reviewed the data and participated in writing of the manuscript. T. Lystig performed statistical analyses and participated in writing of the manuscript. Collection of the data and the statistical analyses were performed by employees of Boehringer Ingelheim. The decision to submit the manuscript involved all authors. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Abstract

Aim: Investigate the long-term effect of tiotropium as first maintenance (MN) respiratory medication in COPD.

Methods: A 4 year randomized multi-center double-blind, parallel-group, placebo-controlled trial (UPLIFT) was conducted. This analysis focused on the effect of tiotropium versus matching placebo in the 810 (13.5%) COPD patients not on other maintenance treatment (MN-naïve: no inhaled LABA, ICS, theophyllines, or anticholinergics) at randomization. Spirometry, health-related quality of life (SGRQ), exacerbations of COPD and mortality were analyzed.

Results: 403 patients patients received tiotropium (age 63±8 years, post-bronchodilator FEV_1 53±12%predicted) and 407 received placebo (age 64+8 years, post-bronchodilator FEV_1 51±12%pred). Post-bronchodilator FEV1 decline was 42±4ml/year in the tiotropium group and 53±4ml/year in placebo (p=0.026). At 48 months, the morning pre-dose FEV1 was 134 ml higher in the tiotropium group compared to placebo (p<0.001). SGRQ total score declined more slowly in the tiotropium group (difference 1.05±0.34 units/year, p=0.002). This was particularly significant for the domains 'impact' (difference 1.08±0.37 units/year, p=0.004) and 'activity' (1.44±0.40 units/year, p<0.001), but not for symptoms (0.26±0.50 units/year, p=0.6). At 48 months, the SGRQ total score was 4.6 units (p<0.001) with tiotropium compared to placebo. Conclusion: In patients with COPD not on maintenance therapy, tiotropium is associated with significant benefits in disease progression.

Trial registration: ClinicalTrials.gov, NCT00144339

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is an increasingly important health problem. In Sweden[1] the 30-year incidence of COPD was reported to be 32% in smokers. More recently, data from the Netherlands determined that the risk to develop COPD in 40 years of follow-up for a non-COPD 55 year old person was 24% for males and 16% for females[2]. Altogether the data indicate that clinicians will continue to be confronted with newly detected patients with COPD.

The main focus of therapy is to relieve symptoms, prevent disease progression, improve exercise tolerance and health status, prevent exacerbations and improve survival, preferably by using interventions with a favourable safety profile[3]. Initial therapy involves preventive measures and often a short-acting bronchodilator to be taken as needed. However, given the known progression of COPD, patients who become symptomatic will eventually require maintenance medications. Present guidelines provide several options for first line maintenance pharmacotherapy, yet sparse data exists as to what outcomes can be expected upon first prescription of initial medication[3]. Particularly knowledge on the long-term effect of pharmacotherapy on lung function, health related quality of life and exacerbations is important to guide the management of these patients and set-up disease management plans for years rather than months.

Studies in patients who are not yet on maintenance respiratory therapy are needed to assist health care professionals in decision making regarding their choice of initial treatment. The Understanding the Potential Long-Term Impacts on Function with Tiotropium (UPLIFT®) trial offers a unique opportunity to gain insight in using tiotropium as a first maintenance drug in COPD. In UPLIFT, patients were randomized and followed for up to four years into a group receiving tiotropium 18 mcg once daily or matching placebo in patients who were permitted use of all maintenance therapies, other than inhaled anticholinergics, as prescribed by their physicians throughout the trial.

The main results of the effect of tiotropium on lung function, health related quality of life, exacerbation rate and mortality are presented elsewhere[4;5].

The aim of the present report was to investigate the clinical outcomes, including disease progression, in patients who were naive to maintenance therapy prior to randomization. Disease progression was evaluated in terms of lung function decline, evolution of health related quality of life (HRQoL), exacerbation rate, survival and the initiation of other concomitant medication during the trial as markers of disease progression.

Methods

Details of the study design were previously reported by Decramer et al.[6] and are summarized below. The primary analysis is reported elsewhere[4].

Study Design

The study was a 4-year, randomized, double-blind, placebo-controlled, parallel-group trial in patients with moderate to very severe COPD. The two co-primary endpoints were yearly rate of decline in pre-bronchodilator (morning pre-study drug) FEV_1 and post-bronchodilator FEV_1 from day 30 (steady state) until completion of double-blind treatment. Secondary outcome measures included the rate of decline in forced vital capacity (FVC) and slow vital capacity (SVC), spirometry at each clinic visit, HRQoL as measured by the St. George's Respiratory Questionnaire (SGRQ) total score, exacerbations (as defined below) and related hospitalizations, and mortality (all-cause and lower respiratory).

The treatment arms were tiotropium 18 mcg once daily or matching placebo delivered via the HandiHaler® inhalation device (Boehringer Ingelheim GmbH & Co. KG, Ingelheim, Germany). In the UPLIFT trial, all patients were permitted to continue or modify respiratory medications, other than inhaled anticholinergics, as prescribed by their physicians, throughout the trial. In the present analysis, the subgroup of patients who were not receiving any maintenance respiratory medications at screening were investigated. This cohort represents 810 subjects of the original 5993 patients included in

UPLIFT (13.5% of the total UPLIFT cohort). The time of initiation of other respiratory drugs was recorded in the case report forms. Smoking cessation was offered to all patients prior to randomization and self-reported smoking behavior was recorded at each visit. Salbutamol could be used as-needed for relief of symptoms.

Participants

Patients were recruited between January 2003 and March 2004 from 490 investigational centers in 37 countries. Patients were recruited from countries in Asia, South America, North America, Europe, South Africa, Australia and New Zealand. Patients were recruited from academic and non-academic medical practices. Criteria for participation included diagnosis of COPD, age ≥40 years, smoking history of ≥10 pack-years, and post-bronchodilator FEV_1 ≤70% of the predicted normal[7] and FEV_1 ≤70% of FVC. Key exclusion criteria were a history of asthma, a COPD exacerbation or respiratory infection within 4 weeks of screening, a history of pulmonary resection, use of supplemental oxygen >12 hours/day, or a significant disease other than COPD which could preclude participation in the study or interfere with the study results. For this analysis, patients on any maintenance respiratory medications (inhaled LABA, ICS, theophyllines, or anticholinergics) were excluded. The protocol was approved by Ethics Committees and all patients provided written informed consent.

Procedures

After a screening period, eligible patients were randomized, using a centralized pseudo random number generator accessed through an interactive voice response system 1:1 to tiotropium or placebo in blocks of four stratified by site. Post-randomization clinic visits occurred at 1 month, at 3 months and then every 3 months throughout the 4-year treatment period.

Spirometry was performed according to American Thoracic Society guidelines[8] at randomization, 30 days and every 6 months throughout the treatment period, and at a follow-up visit approximately 30 days after the end of study treatment. Prior to spirometry testing, respiratory medications were withheld as follows: study drug (24 hours); inhaled steroids morning dose (12 hours); short-acting beta-agonists (8 hours); short-acting (bid or qid) theophyllines and long-acting beta-agonists (including fixed combination with inhaled steroids) (24 hours); and once-daily theophyllines (48 hours). Spirometry was performed prior to (pre-bronchodilator) bronchodilator administration and 90 minutes post bronchodilator (i.e. following bronchodilator administration using 4 actuations of ipratropium [total 80 mcg] followed by 4 actuations of albuterol [total 400 mcg] 60 minutes later). Study drug was administered immediately after pre-bronchodilator spirometry and just prior to short-acting bronchodilator administration. Sites were provided with identical spirometry equipment and study specific software.

HRQoL was measured using the SGRQ[9] prior to pre-bronchodilator spirometry testing at baseline and every 6 months. Adverse events were collected at each visit.

Exacerbations were defined as an increase in or new onset of more than one respiratory symptom (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three or more days requiring treatment with an antibiotic and/or systemic steroid. Data from exacerbations and related hospitalizations were collected on study-specific case report forms at every visit.

Concomitant respiratory maintenance medications and the date at which they were started were retrieved from the case report forms as reported by the treating physician. Classes of respiratory maintenance medication were inhaled corticosteroids (ICS), inhaled long acting beta-2-agonists (LABA), combinations of inhaled steroids and long acting beta agonists (LABA/ICS) either fixed or using the two products separately and theophyllines.

Statistical methods

The statistical methods to analyze the end-points have been described earlier[4]. The present study used the same approach for all its statistical analysis, other than the analyses being restricted to the specified sub-set of patients. Briefly, FEV_1 and vital capacity decline were analyzed using a normal random-effects model in which the measurement changed linearly after day 30 for each subject, where the intercepts and slopes among subjects were assumed to be random with an arbitrary covariance matrix, and with a fixed treatment effect[10]. All randomized and treated patients who were maintenance naïve at baseline were included in these analyses if they had at least 3 lung function assessments from day 30 onward. Health related quality of life (SGRQ total score and its subdomains) were analyzed using the same technique (from 6 months until

completion of treatment). At least two SGRQ assessments were needed from month 6 onward to be included in these analyses. As likelihood-based methods were employed to handle missing data for the random coefficient regression analysis, no imputation was necessary. Analyses of heterogeneity of subgroups were assessed by testing for interaction between treatment group slope and each baseline factor. The mean effects at various visits were compared across treatment groups using repeated measures analysis of covariance without imputation of missing values. SGRQ data from Turkey were excluded due to incorrect validation of the questionnaire.

The time to first exacerbation and associated hospitalization were compared between treatment groups using log-rank tests and were pre-specified as the key secondary analyses. Cox regression was used to derive hazard ratios (HR). The number of events and event days were compared between treatment groups using Poisson regression with correction for treatment exposure and overdispersion[11].

Incidence rates were computed as number of patients with events divided by time at risk. For survival, both an on-treatment and intent to treat analyses were carried out.

Possible differences in baseline variables between treatment groups were evaluated using unpaired t-tests for continuous variables, normal approximation to binominal tests for binary data, and Pearson chi-square tests for other categorical data. These tests were also used to evaluate possible differences in baseline variables between patients on maintenance therapy and those naïve to maintenance therapy.

All reported p-values are two-sided and not adjusted for multiple testing; the nominal alpha was set a priori at 0.05.

Results

A total of 810 patients not receiving maintenance respiratory medications at baseline were identified (403 tiotropium, 407 placebo) (Figure 1). Compared to those that had been treated with maintenance therapies at baseline, the maintenance naïve group was younger, included more smokers, had a shorter history of COPD, and had better lung function (Table 1). The geographic distribution of patients differed between the maintenance naïve group and those treated with maintenance therapies. There were proportionally more Europeans, but proportionally fewer persons from the USA and Latin America (the percentages from Asia were similar). All of these differences described were highly statistically significant ($p<0.0001$).

While the maintenance naïve group as a whole differed markedly from those that were not maintenance naïve, the tiotropium and placebo groups were well balanced within each of the two maintenance therapy categories. When considering region as a whole among those who were maintenance naïve, the Pearson chi-square test for association between region and treatment group was non-significant (Chi-square=7.94, $p=0.0938$). In the maintenance naïve study population there were slightly more Asian ($p=0.04$) and slightly less Western European ($p=0.03$) subjects in the tiotropium group compared to the placebo group.

A slightly lower proportion of patients prematurely discontinued the trial in the tiotropium group (38.0% vs. 43.0% $p=0.14$).

Baseline characteristics of the maintenance naïve patients

Baseline characteristics were balanced between treatment groups (Table 1). Approximately 73% of patients were men and mean age was 63±8 years and 43.1% were active smokers. Patients, on average, had moderate airflow obstruction (post-bronchodilator FEV_1 52±12% predicted) with significant bronchodilator response. FEV_1 increased by 21±17% of the pre-bronchodilator value after the inhalation of ipratropium and salbutamol. The majority of patients were in GOLD II and III with only 5% having GOLD stage IV. Their baseline SGRQ total score was 41±18 units.

Lung function

Lung function variables throughout the trial are given in **Table 2**. After 30 days of treatment, pre-bronchodilator (trough) FEV_1 was 99±15 ml ($p<0.0001$) larger in tiotropium compared to placebo. Trough FEV_1 remained significantly larger in tiotropium compared to control throughout the trial ($p<0.05$ at all time points), with a benefit ranging from 99 to 160 ml (**Figure 2**). Annual decline in lung function after the first month of treatment was slower in the tiotropium compared to placebo.

Health related Quality of life

HRQoL improved in the tiotropium group compared to the placebo group. SGRQ total score improved in the first 6 months in both groups, but the improvement was -2.29 [95%CI -3.94 to -0.65, p=0.0065) units larger in the tiotropium group (Figures 3 and 4). The difference between both groups was also significant for the all domains of the SGRQ (Figure 3). The annual decline in HRQoL after month 6 was faster in the placebo group

compared to tiotropium. The total score of the SGRQ declined by 1.71±0.24 units.yr^{-1} in the placebo and 0.66±0.23 units.yr^{-1} in the tiotropium groups (p=0.0019 between groups). As a consequence, the difference between groups increased over time and reached -4.57 [95%CI -7.06 to -2.09] units.yr^{-1} after 4 years of treatment (**Figure 3**). Decline in symptom score was not different between groups, whereas the differential decline in the impact (-1.08±0.37 units.yr^{-1}, p=0.004) and the activity (-1.44±0.40 units.yr^{-1}, p=0.0004) domain significantly favored the tiotropium group.

Exacerbations

In the placebo and tiotropium groups, 56.5 and 55.6% of the participants respectively experienced at least one exacerbation. The exacerbation rate with tiotropium was 16% lower than with placebo but this did not reach statistical significance (0.49 exacerbations.yr^{-1} with tiotropium, 0.58 exacerbations.yr^{-1} with placebo, p=0.08, Figure 1 in the on-line supplement). The time to the first exacerbation did not differ significantly between groups: 26.9 [95%CI 20.2 to 33.0] months in tiotropium versus 20.6 [17.5 to 25.2; p=0.24 vs placebo] months in placebo. Only 17% of patients experienced an exacerbation leading to a hospital admission. No significant differences were observed between groups.

Mortality

In the placebo group, 56 (13.8%) patients died during the study while on treatment. In the tiotropium group, 44 (10.9%) of patients died (hazard rate 0.74, (95% CI 0.50 to 1.10), p=0.14, Figure 2 on-line supplement). Using an intent to treat analysis, including also

patients who dropped out from the study, these percentages were 15.7% for placebo and 12.2% for tiotropium, (HR 0.76 (95%CI 0.53 to 1.11), p=0.16). On treatment mortality due to lower respiratory tract disorders was 5.2% and 3.2% in the placebo and tiotropium groups respectively (hazard rate 0.59, (95% CI 0.29 to 1.17), p=0.13).

Initiation of other respiratory maintenance therapy

In the tiotropium group 37% of the patients completed the study without taking any concomitant LABA and/or ICS throughout the study. In the placebo group this was 28% of the initially enrolled patients. The remainder of the patients prematurely discontinued participation in the trial or started using at least one of these maintenance therapies before the end of the trial. The hazard rate to start inhaled corticosteroids was 0.76 [95%CI 0.61 – 0.94, p=0.01], the hazard ratio to start long-acting beta agonists was 0.72 [95%CI 0.57 – 0.91, p=0.006] and the hazard rate to start combinations of long acting beta agonists and inhaled steroids was 0.77 [95%CI 0.60 – 0.99, p=0.04] (all $p<0.05$). The subsequent on trial use of both long acting bronchodilators and inhaled corticosteroids was 31.9% in the placebo group and 25.8% in the tiotropium group.

Discussion

The present report, a secondary analysis of a specific subgroup of patients from the UPLIFT study shows evidence of a slowing down of COPD progression in patients in whom tiotropium is started as the first maintenance respiratory drug. This is supported by a better preserved and slower declining lung function and health related quality of life. The study shows, as expected, an initial treatment effect, but the effect becomes larger over time. After four years of treatment patients in the tiotropium group showed a clinically important difference in health related quality of life. In addition trough FEV_1 was 134 ml better in patients treated with tiotropium compared to control subjects and post-bronchodilator FEV_1 (i.e. following inhalation of study drug and 4 actuations of both ipratropium and salbutamol) was 96 ml larger in those patients treated with tiotropium.

The present study investigates a relatively small (13.5%) but particularly interesting sample of patients randomized in the UPLIFT trial. Due to the large sample size of the UPLIFT study, the relatively small proportion of patients still yields an appreciable sample size (n=810) of a clinically interesting subgroup of patients with COPD recruited into clinical trials: patients naive to maintenance respiratory therapy at inclusion. This group of patients is particularly interesting for clinicians faced with the choice of prescribing a first maintenance treatment to patients with COPD.

In the UPLIFT study, patients were allowed to take all concomitant maintenance respiratory therapy as prescribed, with the exception of inhaled anticholinergic agents.

Permitted medications included inhaled corticosteroids, long-acting beta agonists, theophyllines and combinations of the aforementioned. Hence UPLIFT investigated the effect of prescribing tiotropium in a broad cohort of COPD patients that were similar to community practice in order for the trial results to be relevant to health care prescribers. In the entire cohort of patients there was a clear benefit of tiotropium in the setting of usual care (other than inhaled anticholinergics) on lung function and health related quality of life, but the rate of decline of these variables was not affected (i.e. tiotropium and placebo patients subsequently declined at a similar rate). While speculative, due to the liberal concomitant medication scheme, the use of other respiratory maintenance drugs[12] may have resulted in a ceiling effect thereby diminishing the magnitude of potential benefit with tiotropium.

In the patients who were naive to maintenance treatment, FEV_1 decline was faster than that observed in the patients on maintenance therapy. In the placebo group the annual pre bronchodilator FEV_1 decline was 45 $ml.yr^{-1}$, whereas this was only 30 $ml.yr^{-1}$ in the patients in the placebo group of the whole UPLIFT cohort. It is acknowledged that there may be confounders such as the rate of smoking cessation as well as other therapies that potentially could influence the magnitude of the results. Several possible explanations can be sought to explain our findings. *First*, it is tempting to speculate that appropriate drug therapy in COPD may counterbalance decline in lung function over time resulting in a ceiling effect for FEV_1 decline in patients who are treated with maintenance respiratory therapy. The present cohort were not receiving maintenance therapy at the beginning of the study and tiotropium or matching placebo was initiated as the initial maintenance

therapy. Furthermore 36% of patients in the placebo group and 47% of patients in the tiotropium group remained 'maintenance naive' for the data included in the analysis of decline in lung function, health-related quality of life and exacerbations, which is a larger proportion than in the complete UPLIFT cohort. *Second*, there is a difference in the geographical origin of patients in this sub-analysis compared to the complete cohort. To our knowledge, however, no data would suggest a different decline in lung function based on geography neither is there evidence of differences in responsiveness to tiotropium. *Third*, the number of current smokers in this cohort of patients was larger than in the formerly reported full UPLIFT cohort (43.1% vs. 29.6%). A secondary analysis of the UPLIFT cohort, showed a steeper decline in lung function in smokers. It is, however, noteworthy that there was no difference in the rate of decline in lung function with tiotropium when smokers where compared to ex-smokers[13]. A *fourth* explanation may be that the lung function of this cohort of patients was still better preserved (52% predicted vs. 47% predicted in the group on maintenance therapy). By consequence the likelihood to have reached a floor effect in lung function decline is smaller in the maintenance naive patients[14]. This explanation can only partially explain the difference as in another pre-planned secondary analysis of the UPLIFT data[15], patients in GOLD-stage 2 (mean post-bronchodilator FEV1 59% predicted) the lung function decline was $35ml.yr^{-1}$, which is less than in the current sub-analysis. Similarly the fact that the present patients were slightly younger may have biased the results[16], but the difference between the present patients and those on maintenance therapy was very small (1.36 years). Most of these patients however, had concomitant medication, rendering the absence of maintenance medication, the first proposed mechanism, the

most plausible explanation. Regardless of the explanation it is clear that patients who received tiotropium had an initial improvement in lung function, as expected, but importantly the subsequent decline in lung function was also improved. The difference between both randomization groups was 10 $ml.yr^{-1}$ before and 11 $ml.yr^{-1}$ after administering full bronchodilation. Although this may seem a small value at first sight, it is comparable to that observed in the post-hoc analysis of salmeterol and fluticasone as reported in the TORCH study[12]. In that study, the decline in FEV_1 of the combination salmeterol and fluticasone was 16 $ml.yr^{-1}$ slower than in the placebo group. In the long-acting beta-agonist and in the inhaled steroid treated groups, it was 13$ml.yr^{-1}$ slower. Together with the acute treatment effect of tiotropium (99 ml which seems to be maintained throughout the study), the total difference between patients treated with placebo and those treated with tiotropium amounts to 134 ml in morning trough FEV_1 after 4 years of treatment or control. Altogether the data strongly suggest that tiotropium, when used as a first maintenance respiratory drug has an effect beyond its acute bronchodilator effect and slows lung function deterioration in COPD.

Another interesting aspect of the current study is the effect on health related quality of life. Few studies have looked at the effect of pharmacotherapy on long term decline in health related quality of life. Collectively the data show an acute effect on health related quality of life. However, the most important effect is seen during the follow-up. The effect of tiotropium treatment after 6 months was below the commonly accepted minimal clinically important difference (MCID) of 4 units (SGRQ score differed -2.29 units between groups). This difference is comparable to that reported in the whole UPLIFT

cohort, and is somewhat smaller than reported in other studies[17;18] with tiotropium or other long acting bronchodilators, which may reflect the increased use of concomitant respiratory medications in UPLIFT relative to earlier trials. Interestingly the decline in health related quality of life was slower in those patients who received tiotropium, and hence the difference between both groups became larger over time. The difference between groups exceeded the MCID (4 units) after 25.5 months and remained above the MCID thereafter. Clearly this illustrates the advantage of long term studies which allow a better insight into the long term effects of respiratory drugs in patients with COPD. The difference in health related quality of life deterioration between groups is comparable to that reported with fluticasone treatment in the ISOLDE trial (1.17units.yr^{-1})[19]. In the ISOLDE trial, however, the overall decline in both groups was much faster (e.g. ISOLDE placebo group 3.17 units.yr^{-1} vs 1.71 units.yr^{-1} in the placebo group of present study). This difference may at least be partially explained by the initial improvement seen by the 2 weeks of prednisolone treatment at the beginning of that study, which subsequently lead to a more rapid deterioration afterwards. In the present study, the placebo group annual decrease in health related quality of life was comparable to that observed in the BRONCUS[20] trial (1.24 units.yr^{-1} in the placebo group). In the BRONCUS trial, another trial where concomitant medication was permitted, no effect on health related quality of life decline was found with 600 mg.day^{-1} of N-acetyl cysteine administration. The annual reduction in the tiotropium group (0.66 units.yr^{-1}) is an important benefit, when put in this context. It is difficult to compare the present data with the data obtained in TORCH as in that study no data on decline in health related quality of life are available. However, the treatment difference after three years of treatment in TORCH was -3.1 [95%CI -4.1 to

-2.1] units in favour of the combination salmeterol + fluticasone treatment compared to placebo, a group not permitted to use tiotropium, inhaled corticosteroids, or long-acting beta-agonists[21]. In the present study, where other respiratory medications were permitted throughout the study, the difference at this time point (**Figure 3**) was significantly larger: -6.86 [95%CI -9.2 to -4.5] units.

The differences in the four domains of the SGRQ also merit attention. The symptom domain shows a rapid effect but the decline in this dimension is unaffected by tiotropium. The 'activity' domain, however is less improved after 6 months, but the decline in the activity domain is slowed down most by tiotropium treatment. This observation, which is consistent with the findings in ISOLDE[19], reinforces the hypothesis that changes in physical activity are an important consequence of COPD[22], and physical activity is likely further reduced as the disease progresses[23]. Importantly, pharmacotherapy may impact this patient reported outcome, but the impact is seen only after sufficient follow-up. Pitta et al. have shown previously that enhancing physical activity may take time in COPD, even after an intervention as powerful as rehabilitation[24]. The present data suggest that physical activity may be a particularly sensitive outcome to address disease progression and the impact of pharmacotherapy in COPD.

The present study did not show significant effects of treatment with tiotropium on overall exacerbation rates. The number of patients experiencing exacerbations was low relative to the total UPLIFT cohort, yielding a lower statistical power for this analysis. Although the reduction of the number of exacerbations per patient year due to tiotropium was 16%,

which is comparable to the reduction seen in the full UPLIFT cohort, this failed to reach statistical significance (p=0.08). The number of patients experiencing an exacerbation was similar between groups, but there was a non-significant trend toward postponement of the first exacerbation (difference=6.3 months, HR [95%CI]=0.90 [0.75 to 1.08, p=0.24). The trends observed justify a larger study in similar patient cohorts as they may be of clinical relevance. Mortality was not statistically significantly different between groups, though the hazard rate was consistent with that observed in the full cohort[5]. Unfortunately the present analysis lacks the power to make final recommendations related to mortality.

These data focus on an important clinical question regarding tiotropium as the initial maintenance treatment in COPD. However, the data presented in this study are a result of secondary analyses of the UPLIFT trial. Subgroup analyses may provide interesting information for clinicians, but should always be interpreted with great caution. They should be used to guide further research rather than to draw final conclusions[25]. Nevertheless, this analysis was planned before unblinding in the statistical analysis plan (published on-line[4]). Due to the large sample size in UPLIFT, a sufficient number of patients are available to draw conclusions on the end points of lung function and health related quality of life. In order to draw valid conclusions regarding exacerbations and mortality, larger numbers of patients are needed. It is nevertheless interesting to note that the reductions in the risk of death were similar to the overall cohort and consistent with a beneficial effect. An important point of discussion is that patients could be prescribed other maintenance therapy during the study. Considering study completion without

prescription of other maintenance therapy as successful treatment, 37% of patients in the tiotropium group and 28% of patients in the patients in the placebo group completed the protocol without starting additional maintenance therapy with either LABA and/or ICS. This further strengthens the present data as the initiation of other maintenance therapy in the placebo group may have biased against finding differences or reduced the magnitude of differences between groups, which may also have contributed to the lack of statistical significance on exacerbations.

In conclusion, the present study investigated the effect of tiotropium inhalation once daily in patients who did not receive other maintenance therapy at inclusion. Tiotropium treatment is associated with improvements in lung function and health related quality of life. Tiotropium was also associated with a slower disease progression in these patients. It also delayed the start of other maintenance medications and was associated with a non-statistically significant lower risk of mortality. The latter finding may be limited by the relatively small sample, but is consistent with the overall study population. A trend was observed for a lower exacerbation rate and the first exacerbation was postponed, albeit non-significantly. The present analysis highlights the importance and need for prospective studies to specifically investigate the effects of pharmacotherapy in maintenance naïve patients.

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Table 1		Maintenance naïve population				UPLIFT population	
		Tiotropium (n=403)	Placebo (n=407)	P-value	All Maintenance Naïve patients (n=810)	All non MN (n=5182)	P-value
Age	years (SD)	63 (8)	64 (8)	0.20	63 (8)	65 (8)	<0.001
Gender	% male/female	73/27	74/26	0.87	73/27	75/25	0.31
smokers	% active	42	44	0.71	43	28	<0.001
BMI	kg/m² (SD)	26 (6)	26 (5)	0.36	26 (6)	26 (5)	0.45
COPD hist.	years (SD)	9 (8)	9 (7)	0.86	9 (7)	10 (7)	<0.001
FEV_1 pre	%predicted (SD)	44 (11)	43 (12)	0.21	44 (12)	39 (12)	<0.001
FEV_1 post	%predicted (SD)	53 (12)	51 (12)	0.08	52 (12)	47 (13)	<0.001
FVC pre	%predicted (SD)	77 (16)	77 (17)	1.00	77 (17)	75 (18)	<0.001
FVC post	%predicted (SD)	90 (16)	90 (17)	0.89	90 (17)	88 (19)	0.007
GOLD Stage	% II	61	59	0.32	60	44	<0.001
	% III	34	35		34	46	
	% IV	4	6		5	9	
Region	Asia	8.2	4.7	0.09	6.4	6.0	<0.001
	Eastern Europe	9.2	7.9		8.5	21.6	
	Latin America	16.6	16.1		16.3	5.3	
	USA	39.7	38.1		38.9	23.5	
	Western Europe	26.3	33.4		29.9	43.7	

Table 1 Baseline characteristics for the patients enrolled in the present analysis. For reference the characteristics of the remaining UPLIFT patients is given. No statistically significant differences are observed between tiotropium treated and placebo treated

patients at baseline. The P-value refers to the comparison of tiotropium versus placebo or the maintenance naïve patients compared to the remaining patients included in UPLIFT.

Table 2 Lung function throughout the trial and decline in pre and post bronchodilator values.

		Day 1 (L)	**1 month** (L)	**4 years** (L)	**Decline** $ml.yr^{-1}$	p-value
FEV1 pre	Plac	1.21 (0.02)	1.25 (0.01)	1.09 (0.01)	-45 (4)	0.049
	Tio	1.25 (0.02)	1.35 (0.01)*	1.22 (0.01)*	-35 (3)	
FEV1 post	Plac	1.44 (0.02)	1.51 (0.01)	1.31 (0.02)	-53 (4)	0.026
	Tio	1.50 (0.02)	1.56 (0.01)*	1.40 (0.01)*	-42 (4)	
FVC pre	Plac	2.73 (0.05)	2.76 (0.02)	2.57 (0.03)	-56 (7)	0.084
	Tio	2.73 (0.04)	2.95 (0.02)*	2.81 (0.03)*	-38 (7)	
FVC post	Plac	3.19 (0.05)	3.25 (0.02)	3.02 (0.03)	-63 (7)	0.081
	Tio	3.20 (0.05)	3.26 (0.02)	3.07 (0.03)	-46 (7)	
SVC pre	Plac	2.86 (0.05)	2.91 (0.02)	2.72 (0.03)	-55 (7)	0.046
	Tio	2.87 (0.04)	3.08 (0.02)*	2.94 (0.03)*	-35 (7)	
SVC post	Plac	3.23 (0.05)	3.31 (0.05)	3.06 (0.03)	-67 (7)	0.006
	Tio	3.24 (0.05)	3.31(0.02)	3.14 (0.03)$^{\#}$	-39 (7)	

Mean and (SEM) of lung function at baseline (Day 1), 1 month after randomization and at the end of the study (4years) in the placebo group (Plac) and the tiotropium group (Tio). The statistical significance of the comparison between both groups at a given time point is given by * ($p<0.001$ or $^{\#}$ $p=0.06$). The annual decline in the lung function parameter (see statistics for calculation) is also given as well as the p-value for the comparison between groups.

Legend to Figures

Figure 1: Disposition of maintenance naïve patients. This sub-analysis focuses on a sub-group of the original UPLIFT trial.

Figure 2: Mean FEV_1 at each clinic visit in the tiotropium (solid line [▲ pre-bronchodilator; ◆ post-bronchodilator]) and placebo group (solid line [■ pre-bronchodilator; ▲ post-bronchodilator]). Dashed the placebo group, solid lines indicate tiotropium.

Figure 3: Mean St.George's Respiratory Questionnaire Score in the tiotropium and placebo groups in the (a) total score, (b) activity domain, (c) symptom domain and (d) impacts domain. Dashed lines (···■···) indicate the placebo group, solid lines (—▲—) indicate tiotropium.

Figure 1

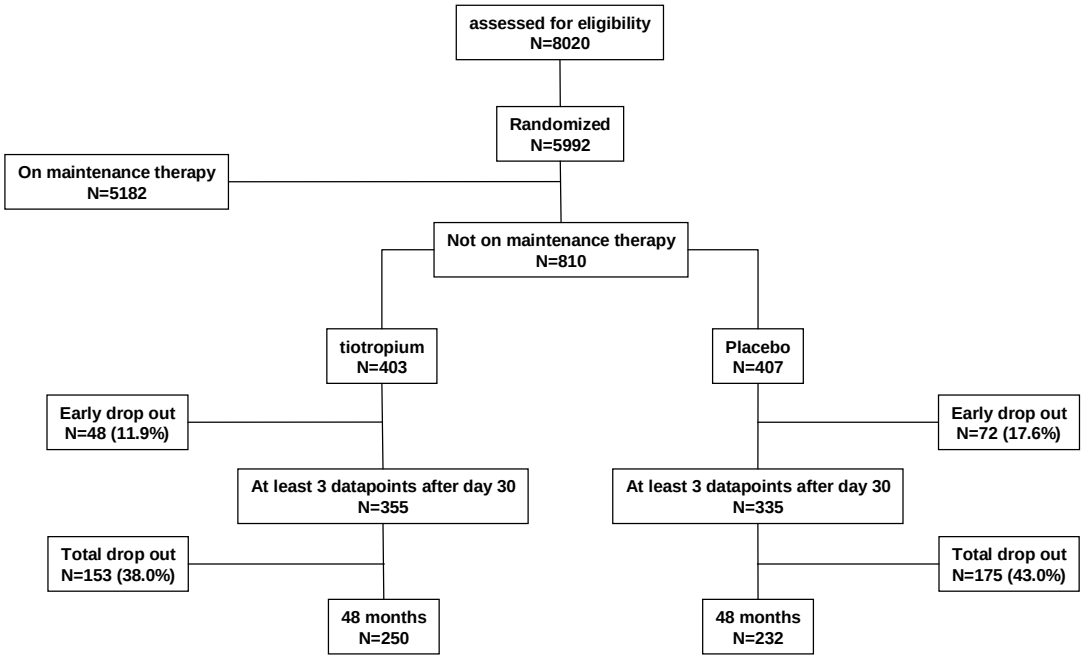
assessed for eligibility
N=8020
Randomized
N=5992
On maintenance therapy
N=5182
Not on maintenance therapy
N=810
tiotropium
N=403
Placebo
N=407
Early drop out
N=48 (11.9%)
Early drop out
N=72 (17.6%)
At least 3 datapoints after day 30
N=355
At least 3 datapoints after day 30
N=335
Total drop out
N=153 (38.0%)
Total drop out
N=175 (43.0%)
48 months
N=250
48 months
N=232

Figure 2

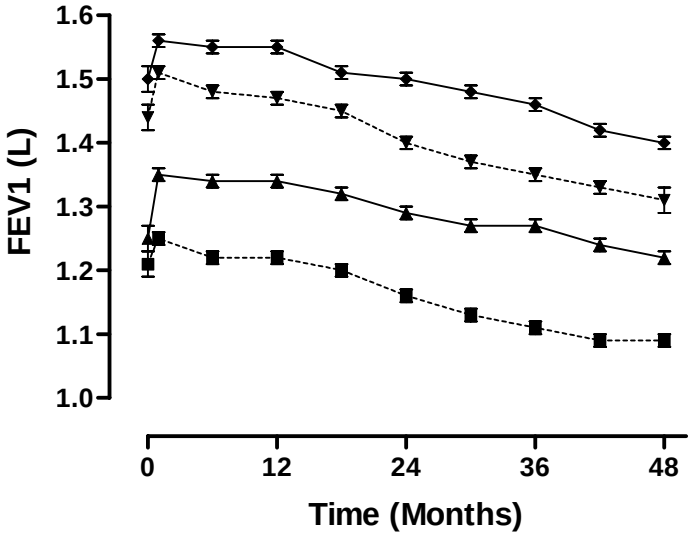

Figure 3a

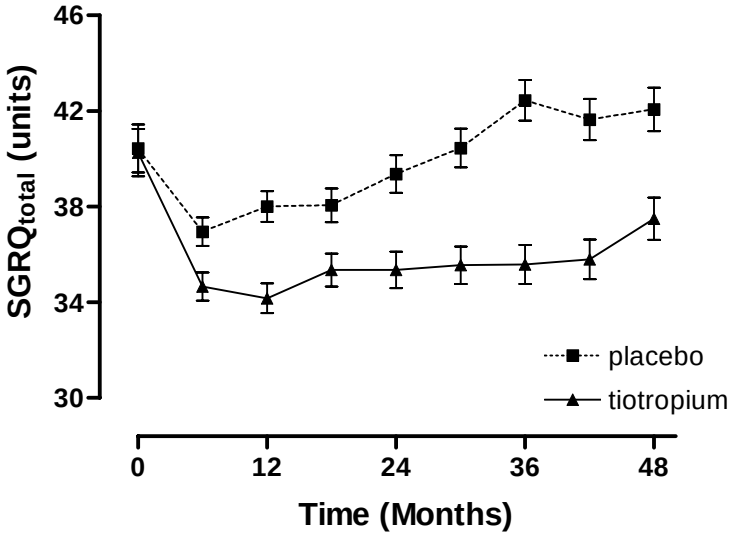
46
42
38
34
30
SGRQtotal (units)
placebo
tiotropium
0
12
24
36
48
Time (Months)

Figure 3b

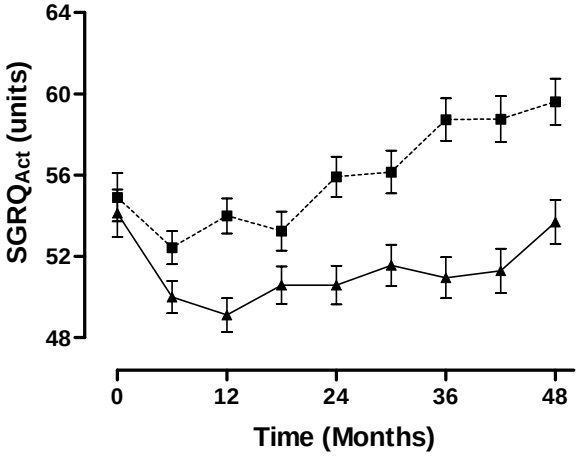

Figure 3c

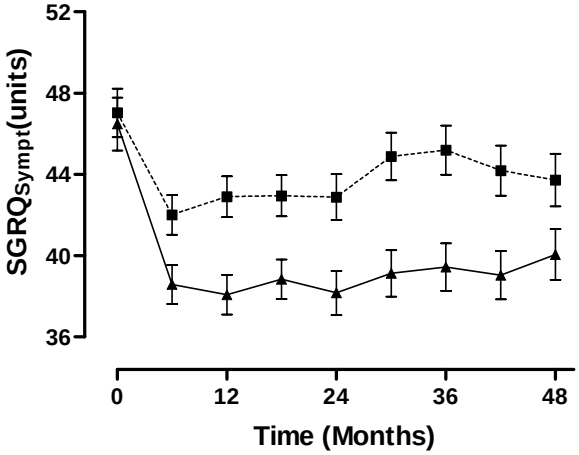

Figure 3d