

Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial



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Summary

Background The beneficial effects of pharmacotherapy for chronic obstructive pulmonary disease (COPD) are well established. However, there are few data for treatment in the early stages of the disease. We examined the effect of tiotropium on outcomes in a large subgroup of patients with moderate COPD.

Methods The Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) study was a randomised, double-blind, placebo-controlled trial undertaken in 487 centres in 37 countries. 5993 patients aged 40 years or more with COPD were randomly assigned to receive 4 years of treatment with either once daily tiotropium (18 µg; n=2987) or matching placebo (n=3006), delivered by an inhalation device. Randomisation was by computer-generated blocks of four, with stratification according to study site. In a prespecified subgroup analysis, we investigated the effects of tiotropium in patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II disease. Primary endpoints were the yearly rates of decline in prebronchodilator forced expiratory volume in 1 s (FEV₁) and in postbronchodilator FEV₁, beginning on day 30 until completion of double-blind treatment. The analysis included all patients who had at least three measurements of pulmonary function. This study is registered with ClinicalTrials.gov, number NCT00144339.

Findings 2739 participants (mean age 64 years [SD 9]) had GOLD stage II disease at randomisation (tiotropium, n=1384; control, n=1355), with a mean postbronchodilator FEV₁ of 1.63 L (SD 0.37; 59% of predicted value). 1218 patients in the tiotropium group and 1157 in the control group had three or more measurements of postbronchodilator pulmonary function after day 30 and were included in the analysis. The rate of decline of mean postbronchodilator FEV₁ was lower in the tiotropium group than in the control group (43 mL per year [SE 2] vs 49 mL per year [SE 2], p=0.024). For prebronchodilator pulmonary function, 1221 patients in the tiotropium group and 1158 in the control group had three or more measurements and were included in the analysis. The rate of decline of mean prebronchodilator FEV₁ did not differ between groups (35 mL per year [SE 2] vs 37 mL per year [SE 2]; p=0.38). Health status, measured with the St George's Respiratory Questionnaire, was better at all timepoints in the tiotropium group than in the control group (p<0.006 for all timepoints). Time to first exacerbation and time to exacerbation resulting in hospital admission were also longer in the tiotropium group than in the control group (hazard ratio 0.82, 95% CI 0.75–0.90, and 0.74, 0.62–0.88, respectively).

Interpretation Tiotropium seemed to reduce the rate of decline of postbronchodilator FEV₁ in patients with GOLD stage II COPD. This finding and the other improvements in outcomes suggest that treatment of COPD should begin at an early stage of the disease.

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Introduction

The introduction of longacting β₂ agonists,¹ inhaled steroids,^{1–5} fixed combination products,^{16–8} and a long-acting anticholinergic drug^{9–12} has substantially improved treatment of patients with chronic obstructive pulmonary disease (COPD). These agents improve pulmonary function and quality of life, and reduce the frequency of exacerbations.^{1–12} Reduction of exacerbations is especially important because they can accelerate the progression of the disease.^{13,14} There are also data to suggest that treatment with a longacting anticholinergic drug¹² and a combination product⁶ might reduce mortality. Additionally, treatment

with a longacting anticholinergic drug was shown to reduce cardiovascular morbidity¹² and incidence of respiratory failure.¹² Most of these studies, however (apart from some that investigated inhaled corticosteroids^{2–4}), mainly included patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage III and IV disease (mean forced expiratory volume in 1 s [FEV₁] ranging from 36% to 45% of predicted value). By contrast, little is known about treatment of COPD at earlier stages, such as GOLD stage II (moderate disease).

One fairly small (n=224) and short-term study showed that in patients with GOLD stage II COPD who were

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recruited in general practice, treatment with tiotropium improved FEV₁ and forced vital capacity (FVC) compared with placebo.¹⁵ Another recent study showed that exercise limitation and dyspnoea were present in patients with

GOLD stage I disease.¹⁶ Studies on activity measurement have consistently shown inactivity early in the disease (ie, GOLD stage I and II).¹⁷⁻¹⁹ Since comorbidities also start early in COPD, there is a case for earlier treatment.²⁰ However, there is currently no clear evidence of the benefit of earlier treatment of COPD, although a recent study suggested that dyspnoea and hyperinflation during exercise could be improved in patients with symptomatic stage I disease with inhaled ipratropium.²¹

We investigated the effect of long-term treatment with tiotropium on outcomes in patients with GOLD stage II COPD, by use of data from the recently published Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial.¹² The UPLIFT trial provided us with the largest group of patients with GOLD stage II disease treated with a longacting anticholinergic drug in a randomised placebo-controlled study.

Methods

Patients

The design and main results of the UPLIFT trial have been reported elsewhere.^{12,22} Briefly, the study was a 4-year, randomised, double-blind, placebo-controlled, parallel-group study in patients with moderate to severe COPD. Patients with a clear diagnosis of COPD, including a differential diagnosis with asthma, were eligible for inclusion. Eligibility criteria also included an age of 40 years or more, a smoking history of 10 pack-years or more, a postbronchodilator FEV₁ of 70% or less of the predicted value, and an FEV₁ of 70% or less of the FVC. Patients were recruited at 487 investigational centres in 37 countries. All patients gave written informed consent for participation in the study. The study protocol was approved by the local ethical review boards of the participating centres.

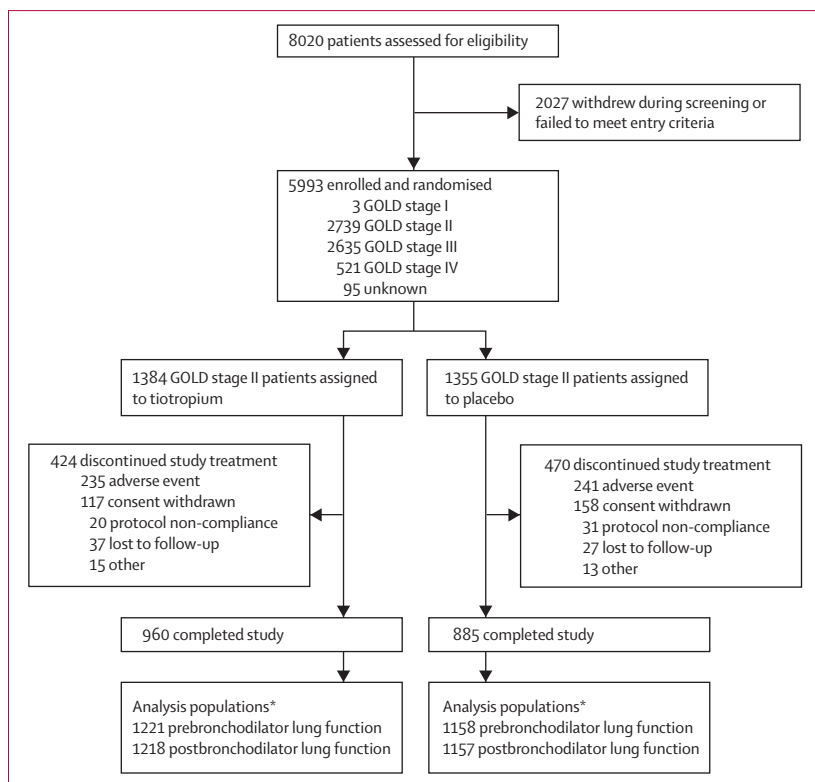


Figure 1: Trial profile for patients with GOLD stage II COPD
 GOLD=Global Initiative for Chronic Obstructive Lung Disease. COPD=chronic obstructive pulmonary disease. *Patients with three or more measurements of pulmonary function after day 30 were included in the analysis of lung function.

	GOLD stage II		GOLD stage III		GOLD stage IV	
	Tiotropium (n=1384)	Control (n=1355)	Tiotropium (n=1304)	Control (n=1331)	Tiotropium (n=250)	Control (n=271)
Male	997 (72%)	979 (72%)	1021 (78%)	991 (74%)	194 (78%)	214 (79%)
Age (years)	65 (9)	64 (9)	65 (8)	65 (8)	62 (8)	63 (8)
FEV ₁ (L)						
Prebronchodilator	1.36 (0.37)	1.36 (0.35)	0.93 (0.26)	0.92 (0.27)	0.59 (0.15)	0.59 (0.15)
Postbronchodilator	1.63 (0.37)	1.64 (0.36)	1.13 (0.27)	1.11 (0.28)	0.71 (0.17)	0.72 (0.16)
FEV ₁ (% predicted)						
Prebronchodilator	49% (8)	49% (8)	33% (7)	33% (7)	21% (4)	21% (4)
Postbronchodilator	59% (6)	59% (6)	40% (6)	40% (6)	25% (4)	25% (4)
Body-mass index (kg/m ²)	27 (5)	27 (5)	26 (5)	26 (5)	24 (5)	24 (5)
Smoking status						
Current smoker	425 (31%)	474 (35%)	371 (28%)	344 (26%)	67 (27%)	66 (24%)
Smoking history (pack-years)	48 (28)	47 (27)	51 (29)	49 (28)	47 (26)	51 (32)
Duration of COPD (years)	10 (8)	9 (7)	10 (7)	10 (7)	11 (8)	10 (6)
SGRQ total score* (units)	41 (17)	42 (17)	48 (16)	48 (16)	56 (15)	56 (16)

Data are n (%) or mean (SD). GOLD=Global Initiative for Chronic Obstructive Lung Disease. FEV₁=forced expiratory volume in 1 s. COPD=chronic obstructive pulmonary disease. SGRQ=St George's Respiratory Questionnaire. *Range 0-100, with lower scores indicating improvement.

Table 1: Baseline characteristics of study participants by GOLD stage

Randomisation and masking

Boehringer Ingelheim arranged for the randomisation as well as packaging and labelling of study medication. Eligible patients were randomly assigned in a 1:1 ratio to receive either 18 µg of tiotropium or a matching placebo, once daily, delivered via the HandiHaler (Boehringer Ingelheim, Ingelheim, Germany). Randomisation was done in blocks of four and stratified according to study site. The randomisation list was generated by use of a validated system, which involved a pseudo-random generator so that the resulting treatment sequence was both reproducible and non-predictable. An interactive voice response system service was used for patient randomisation and drug supply management. Each site was provided with a telephone number (with 24-h access) and password that connected them to a series of instructions on how to assign a medication kit to a patient. The powder capsules were provided in blister cards. The masking of the study drug was such that the treatments were indistinguishable. The treatment codes were kept by Boehringer Ingelheim and were not available to patients or investigators apart from in an emergency situation when the identity of the study drug was needed to be known by the investigator to provide appropriate medical treatment. All concomitant respiratory drugs, apart from inhaled anticholinergic drugs, were allowed during the trial.

Procedures

After randomisation, patients were seen at the clinic at 1 month and 3 months and then every 3 months until the end of the 4-year study period. Primary endpoints were the yearly rate of decline in prebronchodilator FEV₁ and in postbronchodilator FEV₁, beginning on day 30 until completion of double-blind treatment. Secondary endpoints were lung function at every visit, health status measured with the St George's Respiratory Questionnaire (SGRQ), exacerbations and exacerbations requiring hospital admission, and mortality from all causes and from lower respiratory tract conditions. This subgroup analysis, which was prespecified in the protocol and the statistical analysis plan, focused on patients with GOLD stage II COPD.

Spirometry was done according to the American Thoracic Society guidelines at randomisation, at 1 month, and then every 6 months until the end of the study period. Before spirometry testing, respiratory drugs were withheld. Prebronchodilator spirometry was done first, followed by the masked administration of study drug. Immediately after, patients received 80 µg ipratropium, followed 60 min later by 400 µg salbutamol. 30 min after administration of salbutamol, postbronchodilator spirometry was done.

Health-related quality of life was measured by use of the SGRQ, which was administered before spirometry. Exacerbations were defined as an increase or new onset of more than one respiratory symptom (cough, sputum, sputum purulence, wheezing, or dyspnoea) lasting for at

	Baseline		During study	
	Tiotropium (n=1384)	Control (n=1355)	Tiotropium (n=1384)	Control (n=1355)
Longacting β agonists*	771 (56%)	751 (55%)	955 (69%)	962 (71%)
Inhaled corticosteroids*	810 (59%)	772 (57%)	996 (72%)	989 (73%)
Combination longacting β agonist and inhaled corticosteroids	627 (45%)	598 (44%)	841 (61%)	827 (61%)
Anticholinergic drugs†	542 (39%)	516 (38%)	484 (35%)	474 (35%)

Data are n (%). GOLD=Global Initiative for Chronic Obstructive Lung Disease. COPD=chronic obstructive pulmonary disease. *Used alone or in combination. †Includes shortacting or longacting anticholinergic drugs (according to the protocol, the use of longacting anticholinergic drugs during the study was restricted to short-term emergency use for life-threatening exacerbations).

Table 2: Concomitant drugs at baseline and at any point during the study in patients with GOLD stage II COPD

	Tiotropium		Control		Difference between tiotropium and control (mL per year [95% CI])	p value
	n	Mean decline (mL per year [SE])	n	Mean decline (mL per year [SE])		
Primary analysis*						
FEV ₁						
Prebronchodilator	1221	35 (2)	1158	37 (2)	2 (-3 to 7)	0.38
Postbronchodilator	1218	43 (2)	1157	49 (2)	6 (1 to 11)	0.024
FVC						
Prebronchodilator	1221	44 (4)	1158	43 (4)	-1 (-12 to 9)	0.82
Postbronchodilator	1218	53 (4)	1157	58 (4)	6 (-5 to 16)	0.29
SVC						
Prebronchodilator	1221	45 (4)	1158	43 (4)	-1 (-12 to 9)	0.83
Postbronchodilator	1218	55 (4)	1157	60 (4)	5 (-5 to 16)	0.32
Sensitivity analysis†						
FEV ₁						
Prebronchodilator	1347	35 (2)	1310	37 (2)	2 (-3 to 7)	0.36
Postbronchodilator	1344	43 (2)	1305	49 (2)	6 (1 to 11)	0.019

FEV₁=forced expiratory volume in 1 s. FVC=forced vital capacity. SVC=slow vital capacity. *Analysis included patients with three or more measurements of pulmonary function after day 30. †Analysis included patients with at least one measurement of pulmonary function after day 30.

Table 3: Annual rates of decline in prebronchodilator and postbronchodilator FEV₁, FVC, and SVC

least 3 days and requiring treatment with an antibiotic, systemic steroid, or both. Data for exacerbations and associated hospital admissions were recorded on case-report forms at every visit.

For all patients who discontinued treatment prematurely, data for vital status were requested on a recorded date determined as the full completion of the trial protocol. Mortality analysis was done with data for on-treatment mortality and for on-treatment mortality plus vital status.

Statistical analysis

The sample size calculation for the study was based on the following assumptions: a difference in rate of decline of 15 mL per year between the two treatment groups,⁴ a standard deviation of 90 mL per year, discontinuation rate of 35%, power of more than 90%, and a significance

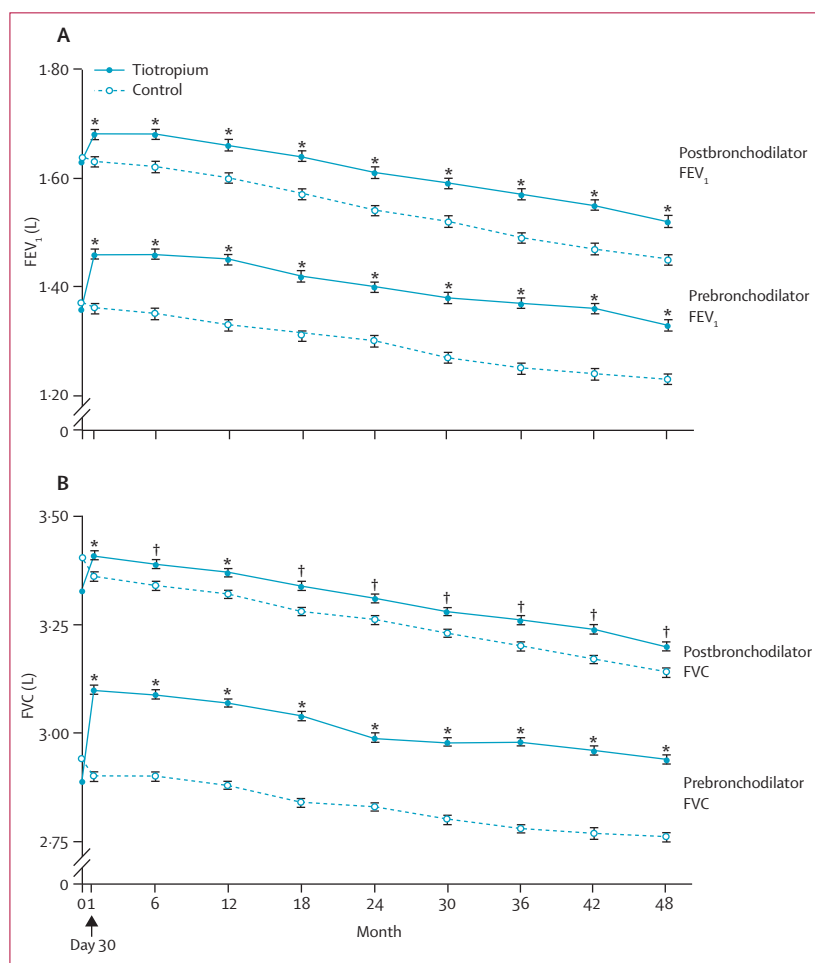


Figure 2: Mean prebronchodilator and postbronchodilator FEV₁ and FVC during the study in patients with GOLD stage II COPD

FEV₁=forced expiratory volume in 1 s. FVC=forced vital capacity. GOLD=Global Initiative for Chronic Obstructive Lung Disease. COPD=chronic obstructive pulmonary disease. **p*<0.0001 versus control. †*p*<0.01 versus control. Repeated measure ANOVA was used to estimate means, which are adjusted for baseline measurements. Patients with three or more pulmonary function tests after day 30 were included in the analysis. Error bars show SEs. (A) FEV₁. Month 0: tiotropium, n=1196; control, n=1142. Month 48: tiotropium, n=925; control n=859. Mean differences between groups range from 101 mL to 119 mL for prebronchodilator FEV₁, and from 52 mL to 82 mL for postbronchodilator FEV₁. (B) FVC. Month 0: tiotropium, n=1196; control, n=1142. Month 48: tiotropium, n=925; control, n=859. Mean differences between groups range from 164 mL to 194 mL for prebronchodilator FVC and from 42 mL to 68 mL for postbronchodilator FVC.

level of 5% with a two-tailed test.²² 1166 patients per group were needed for the primary analysis. The sample size was increased to approximately 6000 patients to allow additional analyses of important patient subgroups.

Decline in pulmonary function versus time was analysed with random coefficient regression in which the FEV₁ changed linearly after 30 days for each patient, intercepts and slopes were random, and the treatment effect was fixed. The population for the primary analysis included all patients who had at least three measurements of pulmonary function after day 30. As a sensitivity analysis, we analysed the patients who had at least one measurement of FEV₁ after day 30. The model used in the primary analysis was also used for decline in SGRQ versus time (from 6 months

until completion of the study). All patients who had at least two measurements of SGRQ were analysed. SGRQ values from Turkey were excluded because of an error in the translation of the questionnaire.

Cox regression was used to calculate hazard ratios (HRs). Kaplan-Meier curves of the probability of no exacerbation and consequent admission to hospital were constructed. 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 done with SAS software, version 8.2. All reported *p* values are two-sided and not corrected for multiple testing. This study is registered with ClinicalTrials.gov, number NCT00144339.

Role of the funding source

A joint advisory committee, which included academic scientists and employees of the study sponsor, was responsible for study design, monitoring of the conduct of the trial, data review and interpretation, approval of the statistical analyses, writing of the report, and the decision to publish the report. Statistical analyses were done by employees of Boehringer Ingelheim. All authors had full access to all the data in the study. The corresponding author had final responsibility for the decision to submit the report for publication.

Results

Of 5993 randomised patients, 2739 (46%) had GOLD stage II COPD (figure 1). A higher proportion of patients in the control group (35%) discontinued study treatment than did patients in the tiotropium group (31%; *p*=0.024). Table 1 shows the baseline characteristics of study participants in the tiotropium and control groups by disease stage. The most relevant concomitant drugs used by patients with GOLD stage II disease at baseline and during the study are shown in table 2.

In the tiotropium group, 1221 patients and 1218 patients were included in the primary analyses for prebronchodilator and postbronchodilator pulmonary function, respectively. In the control group, 1158 patients and 1157 patients were analysed, respectively. Table 3 shows the rates of decline in lung function in the study groups.

Prebronchodilator FEV₁ declined by a mean of 35 mL per year (SE 2) in the tiotropium group compared with 37 mL per year (SE 2) in the control group (*p*=0.38). For postbronchodilator FEV₁, the rate of decline was lower in the tiotropium group than in the control group (43 mL per year [SE 2] vs 49 mL per year [SE 2], *p*=0.024). For FVC and slow vital capacity (SVC), the rates of decline of prebronchodilator values did not differ between groups. However, the rates of decline after bronchodilation were lower in the tiotropium group than in the control group, although not significantly so.

In an additional sensitivity analysis, we included all patients who had at least one measurement of FEV₁ after

day 30. The results of this analysis were consistent with those seen in the primary analysis (table 3).

Mean values of prebronchodilator and postbronchodilator FEV₁ were higher in the tiotropium group than in the control group at all timepoints during the trial ($p < 0.0001$ for all timepoints), with differences between groups ranging from 101 mL to 119 mL and from 52 mL to 82 mL, respectively (figure 2). Mean prebronchodilator FVC was 164–194 mL higher (figure 2) and mean prebronchodilator SVC was 44–175 mL higher in the tiotropium group than in the control group ($p < 0.001$ at all timepoints). Differences for postbronchodilator FVC and SVC ranged from 42 mL to 68 mL ($p < 0.01$ at all timepoints) and from 15 mL to 35 mL ($p > 0.05$ at all timepoints), respectively.

In both groups, SGRQ scores decreased relative to baseline over the first 6 months, corresponding with an improvement in health status (figure 3). Thereafter, there was a progressive increase in the scores in both groups, corresponding with a deterioration in health status. This deterioration occurred at similar rates in the two groups (total SGRQ score: tiotropium, 0.89 units per year [SE 0.13]; control, 0.99 units per year [SE 0.13]; $p = 0.58$). Health status was better at all timepoints in the tiotropium group than in the control group ($p \leq 0.006$ at all timepoints, for the total score and three subscores; figure 3). Differences in SGRQ scores between groups ranged from 2.7 to 4.0 units for the total score and from 2.3 to 3.9 units, 2.7 to 4.1 units, and 3.1 to 4.4 units for the subscores of impact, symptom, and activity, respectively.

Table 4 shows the number of exacerbations and table 5 shows the number of exacerbations resulting in hospital admission in patients with GOLD stages II–IV. Data for the total study population have been reported elsewhere.¹² In patients with COPD that was GOLD stage II or III, risk of exacerbation and number of exacerbations per patient-year were lower in the tiotropium group than in the control group. Despite the low event rates, these differences reached statistical significance because of the high power of this study. There was no interaction between the treatment effect on exacerbations and GOLD stage ($p = 0.237$) or baseline SGRQ score ($p = 0.677$).

The risk of an exacerbation requiring admission to hospital in patients with GOLD stage II COPD was also lower in the tiotropium group than in the control group. The mean number of exacerbation-related hospital admissions per patient-year was also lower, but the difference was not significant. A further subgroup analysis suggested that the risk of an exacerbation was lower in the tiotropium group than in the control group in patients taking inhaled corticosteroids at baseline (HR 0.85, 95% CI 0.76–0.96, $p = 0.0098$) and in patients not taking these agents at baseline (0.76, 0.65–0.89, $p = 0.0006$).

The effects of tiotropium on mortality for the whole study population have been reported elsewhere.¹² In

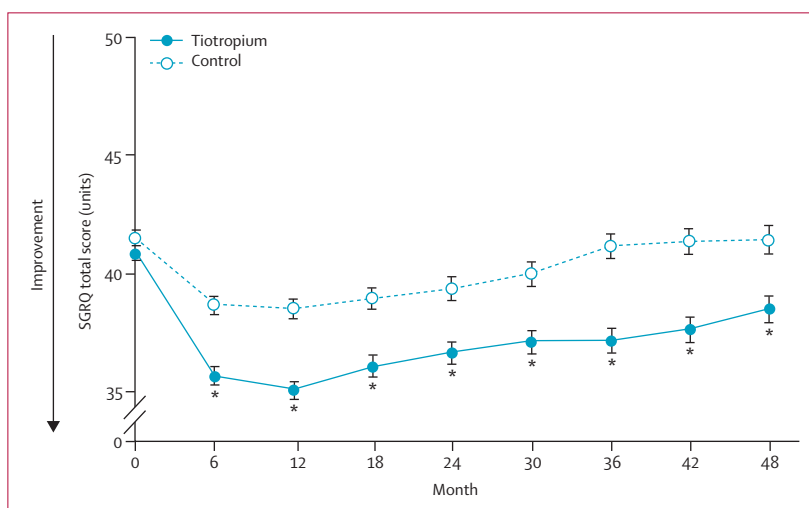


Figure 3: Mean SGRQ score during the study in patients with GOLD stage II COPD

SGRQ=St George's Respiratory Questionnaire. GOLD=Global Initiative for Chronic Obstructive Lung Disease. COPD=chronic obstructive pulmonary disease. The SGRQ scale ranges from 0 to 100, with lower scores indicating improvement. * $p < 0.0001$ versus control. Repeated measure ANOVA was used to estimate means, which are adjusted for baseline measurements. Patients with two or more SGRQ total scores after month 6 were included in the analysis. Error bars show SEs. Month 0: tiotropium, $n = 1179$; control, $n = 1119$. Month 48: tiotropium, $n = 908$; control, $n = 839$. Mean differences between groups range from 2.7 to 4.0 units.

	Tiotropium	Control	Ratio (95% CI)*	p value
One or more COPD exacerbations (n/N [%])				
GOLD stage II	824/1384 (60%)	882/1355 (65%)
GOLD stage III	944/1304 (72%)	942/1331 (71%)
GOLD stage IV	200/250 (80%)	188/271 (69%)
Median time to first exacerbation (months [95% CI])				
GOLD stage II	23.1 (21.0–26.3)	17.5 (15.9–19.7)	0.82 (0.75–0.90)	<0.0001
GOLD stage III	13.2 (11.5–14.6)	9.8 (8.8–11.3)	0.87 (0.79–0.95)	0.002
GOLD stage IV	9.7 (8.2–12.0)	8.8 (6.9–11.7)	0.99 (0.81–1.21)	0.956
Mean number of exacerbations (per patient-year [95% CI])				
GOLD stage II	0.56 (0.52–0.60)	0.70 (0.65–0.75)	0.80 (0.72–0.88)	<0.0001
GOLD stage III	0.85 (0.80–0.90)	0.97 (0.91–1.03)	0.88 (0.80–0.95)	0.003
GOLD stage IV	1.05 (0.92–1.21)	1.15 (1.00–1.31)	0.92 (0.76–1.12)	0.397

GOLD=Global Initiative for Chronic Obstructive Lung Disease. COPD=chronic obstructive pulmonary disease. *Hazard ratio for time to first exacerbation and rate ratio (tiotropium to control) for number of exacerbations.

Table 4: Exacerbations in patients with GOLD stage II, III, or IV COPD in the tiotropium and control groups

patients with GOLD stage II COPD, risks of mortality from lower respiratory tract conditions and from all causes were lower for the tiotropium group than for the control group during treatment (table 6). Similar results were obtained in analyses that included data for vital status from patients who had discontinued study treatment before the end of the study (table 6). However, differences between groups were not significant. Similar reductions were seen in patients with GOLD stage III and IV: at day 1470, the HRs for all-cause mortality were 0.86 (0.71–1.05) and 0.76 (0.53–1.09), respectively.

Serious adverse events associated with tiotropium treatment have been reported elsewhere.¹²

	Tiotropium	Control	Ratio (95% CI)*	p value
One or more COPD exacerbations resulting in admission to hospital (n/N [%])				
GOLD stage II	211/1384 (15%)	264/1355 (19%)
GOLD stage III	421/1304 (32%)	413/1331 (31%)
GOLD stage IV	112/250 (45%)	116/271 (43%)
Median time to first exacerbation resulting in admission to hospital, first quartile (months [95% CI])				
GOLD stage II	Not estimable	Not estimable	0.74 (0.62–0.88)	0.001
GOLD stage III	25.2 (22.3–29.2)	22.7 (18.9–26.3)	0.93 (0.81–1.06)	0.270
GOLD stage IV	13.6 (10.6–18.3)	11.1 (7.8–17.1)	0.85 (0.66,1.10)	0.225
Mean number of exacerbations resulting in admission to hospital (per patient-year [95% CI])				
GOLD stage II	0.08 (0.07–0.09)	0.10 (0.08–0.12)	0.80 (0.63–1.03)	0.082
GOLD stage III	0.20 (0.18–0.22)	0.21 (0.18–0.23)	0.97 (0.81–1.15)	0.705
GOLD stage IV	0.35 (0.28–0.44)	0.35 (0.28–0.45)	0.99 (0.72–1.37)	0.963

GOLD=Global Initiative for Chronic Obstructive Lung Disease. COPD=chronic obstructive pulmonary disease. *Hazard ratio for time to first admission and rate ratio (tiotropium to control) for number of admissions.

Table 5: Exacerbations resulting in hospital admissions in patients with GOLD stage II, III, and IV COPD in tiotropium and control groups

	Tiotropium (n=1384)	Control (n=1355)	HR (95% CI)
All-cause mortality			
Patients on treatment	117 (8%)	130 (10%)	0.85 (0.66–1.09)
Patients on treatment and discontinued patients			
Protocol-defined treatment period (up to day 1440)	128 (9%)	147 (11%)	0.84 (0.66–1.07)
Period including 30-day washout period (up to day 1470)	134 (10%)	148 (11%)	0.88 (0.69–1.11)
Mortality from lower respiratory tract conditions			
Patients on treatment	15 (1%)	23 (2%)	0.62 (0.32–1.18)
Patients on treatment and discontinued patients			
Protocol-defined treatment period (up to day 1440)	20 (1%)	24 (2%)	0.81 (0.45–1.46)
Period including 30-day washout period (up to day 1470)	20 (1%)	25 (2%)	0.77 (0.43–1.39)

GOLD=Global Initiative for Chronic Obstructive Lung Disease. COPD=chronic obstructive pulmonary disease.

Table 6: Deaths in patients with GOLD stage II COPD, by analysis population

Discussion

This subgroup analysis of the UPLIFT trial showed that in patients with GOLD stage II COPD, tiotropium seemed to reduce the rate of decline of postbronchodilator FEV₁ and the risk of exacerbations. Additionally, lung function and health-related quality of life were better in the tiotropium group than in the control group throughout the trial. Our findings suggest that treatment with a longacting anticholinergic drug has substantial benefits in patients with moderate COPD, and therefore provide a rational basis for starting treatment in patients with this stage of the disease. The reduction in the rate of decline in postbronchodilator FEV₁ is of particular interest because it has potential to alter the natural course of the disease in this early stage, although the effect in this study was small and might not be clinically significant.

A substantial proportion of patients with COPD diagnosed by spirometry receive suboptimum treatment.^{23–25}

In a prospective study, patients admitted to a general medicine service were asked to undergo spirometry and answer a questionnaire. Of the 153 participants, 40 (26%) had airflow obstruction, of whom only 14 (35%) were diagnosed with COPD at the time of admission to hospital. Only 14 (35%) patients with airflow obstruction were receiving maintenance bronchodilator treatment at hospital admission or discharge.²⁴ In a study in a primary-care setting in Japan that included 194 patients who had chronic cough and sputum but no previous diagnosis of respiratory disease, 96 had at least moderate (GOLD stage II) COPD. However, 30 (31%) did not receive any clinical intervention, defined as advice to stop smoking or pharmacotherapy, or both.²⁵ Data showing that patients with stage II disease can benefit from treatment might encourage health-care providers to accurately diagnose and treat patients according to international guidelines.

This analysis has several limitations. First, although the subgroup analyses were prespecified, this study is a subgroup analysis of a large trial and therefore is associated with all the typical methodological concerns of such an analysis. Second, although all patients in this analysis had GOLD stage II COPD, they might not have been representative of all patients with this stage of the disease. Because we recruited patients from pulmonary practices, they might have more severe disease than do patients that usually present to general practice. Additionally, the inclusion criteria required patients to have a postbronchodilator FEV₁ of 70% or less than the predicted value and therefore patients with less severe GOLD stage II disease (FEV₁ between 70% and 80% of the predicted value) were excluded. This hypothesis is supported by the mean postbronchodilator FEV₁ of 59% of the predicted value recorded in this study. Moreover, because the patients in this analysis were seen by pulmonary specialists, they were also likely to present with symptoms; therefore, asymptomatic patients with GOLD stage II disease might have been excluded. However, symptomatic patients with GOLD stage II disease pose a substantial clinical problem because of the clear impairment in health status as shown by the high baseline SGRQ score and the propensity for exacerbations of COPD. Notably, most patients in both groups were on concomitant treatment with inhaled corticosteroids, longacting β_2 agonists, or both, suggesting that the treatment effects were obtained irrespective of other active agents.

A prospective, double-blind, placebo-controlled trial in patients with GOLD stage II COPD who are identified in general practice by use of spirometry and symptom questionnaires²⁶ would provide the strongest possible rationale for earlier intervention with a longacting bronchodilator. Nevertheless, this report provides strong evidence for such an intervention. Other published reports provide indirect evidence that lends support to earlier treatment. Ofir and colleagues¹⁶ showed that

symptomatic patients with GOLD stage I disease had exercise limitation and dyspnoea¹⁶ and that pharmacotherapy reduced hyperinflation and dyspnoea in these patients.²¹ Hyperinflation and dyspnoea during exercise might contribute to inactivity in the early stages of the disease—a frequent finding in other recent studies.^{17–19} Comorbidities such as cardiovascular disease, osteoporosis, and diabetes²⁰ are also present in patients with early stages of COPD. These comorbidities could be alleviated through more active treatment of COPD, in addition to specific treatment.

Recent studies have suggested that the annual decline in FEV₁ is greater in GOLD stage II than in later stages of the disease.^{14,27} If the decline in pulmonary function predominantly occurs early in the course of the disease, then it is logical that intervention aimed at reducing the progression of the disease should mainly occur in the early stages of the disease. The effectiveness of aggressive early treatment needs to be assessed in prospective studies that compare this approach with treatment of symptoms alone.

The mean age of patients with GOLD stage II COPD was similar to that for the whole study population and for patients with GOLD stage III and IV disease. Although it is not known how representative the present study populations are for the entire COPD populations in the different GOLD stages, this finding suggests that COPD does not progress from one GOLD stage to the other. Longitudinal cohort studies could provide further understanding of the mechanisms of progression of COPD.

Thus, in patients with GOLD stage II COPD, long-term treatment with tiotropium seemed to reduce the rate of decline of postbronchodilator FEV₁ and the risk of exacerbations. Since we also found that lung function and health-related quality of life were better in the tiotropium group than in the control group throughout the trial, treatment of COPD should begin in symptomatic patients with moderate disease.

Contributors

MD, BC, SK, SM, and DPT participated in study design, monitoring of the conduct of the trial, data review, data interpretation, and writing of the report. MD wrote the first draft of the report and the final content was developed in collaboration with all authors. TL participated in the statistical analysis of the subgroup data. All authors saw and approved the final version of the report.

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Conflicts of interest

MD has received consulting fees from Boehringer Ingelheim, Pfizer, GlaxoSmithKline, and Nycomed, lecture fees from Boehringer Ingelheim and Pfizer, and grant support from AstraZeneca. 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. SM was an employee of Pfizer at the time of submission. 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, Pfizer, and Sepracor.

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