Title

Annual rates of change in pre- vs. post-bronchodilator FEV1 and FVC over 4 years in moderate to very severe COPD

Journal

Respiratory Medicine, 107(12)

ISSN

0954-6111

Authors

Tashkin, Donald P
Li, Ning
Halpin, David
et al.

Publication Date

2013-12-01

DOI

10.1016/j.rmed.2013.08.001

Peer reviewed

Published in final edited form as:
Respir Med. 2013 December ; 107(12): 1904–1911. doi:10.1016/j.rmed.2013.08.001.

Annual rates of change in pre- vs. post- bronchodilator FEV1 and FVC over 4 years in moderate to very severe COPD

Donald P. Tashkin, MD[1], **Ning Li, PhD**[1], **David Halpin, MD**[2], **Eric Kleerup, MD**[1], **Marc Decramer, MD**[3], **Bartolome Celli, MD**[4], and **Robert Elashoff, PhD**[1]

[1]David Geffen School of Medicine at UCLA, 10833 Le Conte Ave., Los Angeles, CA 90095, USA

[2]Royal Devon and Exeter Hospital, Barrack Road, Exeter EX2 5DW, UK

[3]University of Leuven, Herestraat 49, B-3000, Leuven, Belgium

[4]Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115, USA

Abstract

While the slope of decline in FEV1 has traditionally been calculated from the post- rather than the pre-bronchodilator measurement in COPD interventional trials, it is not clear whether and to what extent these two slopes differ in symptomatic patients with COPD. Therefore, we used data from the 4-year UPLIFT trial of tiotropium 18 mcg QD vs. placebo to compare annual rates of change in pre- vs. post-bronchodilator FEV_1 in 5041 patients with moderate to very severe COPD (mean FEV_1 48% pred) in whom the post-bronchodilator FEV1 was measured after 4 inhalations of two different classes of short-acting inhaled bronchodilators at baseline and 1 month and every 6 months post-randomization over 4 years. Linear mixed effects models were used to estimate annual rates of decline in FEV_1 and FVC pre- and post- bronchodilator in each treatment group separately, after adjusting for height, gender, smoking status, baseline % predicted FEV_1 or FVC, and baseline acute % improvement in lung function. The slopes of the post-bronchodilator FEV_1 and FVC were significantly steeper than the pre-bronchodilator slopes regardless of treatment arm ($p < 0.001$), while the estimated variances of the slopes were similar. Post-bronchodilator increases in FEV1 and FVC diminished progressively and significantly ($p < 0.0001$) over the 4-year trial, suggesting a possible explanation for the significant differences between the pre- and post-bronchodilator slopes. While the reasons for these differences are not completely clear, they are important to consider when assessing treatment effects on rates of decline in FEV1 and FVC.

Keywords

slope of FEV1 decline; post-bronchodilator; COPD; UPLIFT

Introduction

For nearly 50 years the rate of progression of COPD has been defined by the slope of the annual decline in FEV1 determined from serial measurements of FEV1 obtained over a span

Corresponding Author: Donald P. Tashkin, MD, Emeritus Professor of Medicine, David Geffen School of Medicine at UCLA, 10833 Le Conte Ave., Los Angeles, CA 90095 USA, 310-825-3163 – office, 310-206-5088 – FAX, dtashkin@mednet.ucla.edu.

of years in the course of observational or intervention studies. In intervention trials conducted over the last few decades, this slope has been determined mainly from serial measurements of the post-, rather than the pre-, bronchodilator FEV1[1-10]. The rationale for the latter practice appears to derive from the assumption that there may be less variability in the post- than the pre-bronchodilator measurement and that the post-bronchodilator value would be less influenced by noncompliance with instructions to withhold bronchodilator medication during the washout period prior to scheduled spirometric testing. However, we recently reported that the slope estimates over 5 years, as well as the standard errors of these estimates, were only slightly higher for the pre- than post-bronchodilator FEV_1 in 4484 Lung Health Study (LHS) participants with mild to moderate airflow obstruction (mean FEV_1 78% predicted)[1]. These findings suggested that serial pre-bronchodilator FEV_1 measurements may be sufficient for comparing the impact of interventions on the annual rates of change in FEV_1. On the other hand, the post-bronchodilator measurements in the LHS were obtained only approximately 15 minutes after only 2 inhalations of a short-acting beta-agonist, suggesting that the FEV_1 response was submaximal. Moreover, results could possibly differ in a more severe COPD population. In order to investigate the latter possibility, we analyzed FEV_1 and FVC measured before and 30-90 minutes after near-maximal doses of two different bronchodilators at baseline and every 6 months over 4 years in a population of patients with more advanced, moderate to very severe COPD (mean FEV1 48% predicted) who were participants in the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) trial of tiotropium 18 mcg Handihaler once daily vs. placebo[9].

Methods

In a post-hoc analysis using data from the UPLIFT trial, we compared annual rates of change in pre- vs. post-bronchodilator FEV_1 in 5041 patients with moderate to very severe COPD (mean FEV_1 48% predicted) in whom the post-bronchodilator FEV1 was measured at the time of expected peak action of 4 inhalations of two different classes of short-acting inhaled bronchodilators (ipratropium, 18 μg/inhalation, followed 1 hour later by albuterol, 100 μg/inhalation, followed 30 min later by spirometry) at baseline and 1 month and every 6 months post-randomization over 4 years.

Analytic methods

Annual rates of change were estimated for the two treatment groups (tiotropium and placebo) separately. Among the 5992 subjects in the original study, the 5041 (84.1%) who had at least 3 serial measurements beginning with the measurement at 6 months were included in this analysis. Baseline characteristics of patients in each group are summarized using descriptive statistics. Comparison of treatment groups was performed using t-tests for normally-distributed continuous data, the Wilcoxon rank-sum test for non-normal continuous variables, and the Chi-square test for categorical variables. Linear mixed effects models were used to estimate annual change in FEV_1 and FVC (ml/yr) measured pre- and post- bronchodilator for each group separately. The model assumed random intercept and random slope to take into account between-subject heterogeneity and estimated the slope (annual decline) using data from 6 months on (rather than from baseline) up to year 4 to

exclude the bump-up in lung function that was observed between baseline and the 6-month visit in both treatment groups. The analysis was also adjusted for height, gender, smoking, baseline % predicted FEV_1 (or FVC), and baseline acute % improvement after bronchodilator administration. Smoking status was categorized as continuing smoking at all visits (n = 629, 12.5%), sustained ex-smoking at all visits (n = 2972, 59.0%) and intermittent smoking (n = 1440, 28.6%). Separate analyses were also performed according to GOLD grades of severity of airflow obstruction I-II, III and IV. All analyses were performed using SAS software v9.2 (Cary, NC).

Written informed consent was obtained from all participants enrolled in the UPLIFT trial. The study was approved by the institutional review boards of each of the participating centers and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study was registered with ClinicalTrials.gov (number NCT00144339).

Results

Of the 5992 subjects enrolled in the UPLIFT trial, 5041 (84.1%) fulfilled criteria for inclusion in the present analysis. The baseline characteristics of these were similar to those of the entire UPLIFT study population[9] and are shown in Table 1. Approximately three-fourths of the participants were male, >90% were Caucasian and their mean age was ∼64 years. Average FEV1 was ∼40% % predicted pre- and ∼48% predicted post-bronchodilator administration. Forty-eight percent of the subjects had mild-moderate airflow obstruction (GOLD grade I-II), 43% severe airflow obstruction (GOLD grade III) and 8% very severe obstruction (GOLD grade IV). Slightly less than 30% were current smokers. No differences were noted between treatment arms.

The slope estimates for the annual change in pre- and post-bronchodilator FEV1 and FVC in ml/yr obtained from the linear mixed effects model are shown in Table 2. Slopes were adjusted for the following covariates: height, gender, smoking status (continuing smoking at all visits sustained, ex-smoking at all visits and intermittent smoking), baseline FEV1 (or FVC) % predicted, baseline % acute improvement in response to bronchodilator administration by treatment group. The observed data for the pre- and post-bronchodilator FEV1 and FVC for each treatment arm are also illustrated in Figure 1 and Figure 2, respectively. The adjusted slope estimates are very similar to those unadjusted for the various covariates (Table 2). The mean slopes determined from the post- bronchodilator FEV1 and FVC are significantly steeper than those calculated from the pre-bronchodilator measurements ($p < 0.001$), the differences being numerically larger for FVC than FEV1 (Table 2). Although the slope differences and their variances, in general, tend to be slightly higher in the placebo than the tiotropium treatment arm, these between-treatment differences are not statistically significant.

Slope estimates for the annual change in pre- and post-bronchodilator FEV1 and FVC stratified by the severity of airflow obstruction (GOLD grades I-II, III and IV) are shown in Table 3a-3c. Numerically, for FEV1 the pre-post bronchodilator slope differences were slightly larger in GOLD grades III and IV compared to GOLD grades I-II, while for FVC

the pre-post bronchodilator slope differences were most pronounced in GOLD grades III and IV.

Discussion

In this population of COPD patients with moderate to very severe airflow limitation participating in a 4-year trial of tiotropium vs. placebo, unlike findings from an earlier study in COPD patients with mild to moderate obstruction[1], the slopes of the post-bronchodilator FEV_1 and FVC are significantly steeper than the slopes calculated from the pre-bronchodilator measurements, while the variances are similar, regardless of treatment arm (Table 2). The differences between the pre- vs. post-bronchodilator slopes of decline in FEV_1 and FVC are numerically greater in GOLD grades III and IV compared to GOLD grades I and II (Table 3a-c).

We hypothesized that a possible reason why the slopes determined from the post- compared to the pre-bronchodilator measurements might be due to reduced bronchodilator responsiveness for both FEV_1 and FVC over time. Consequently, we examined the absolute changes (milliliters) in FEV1 and FVC at each time point over the 4-year trial beginning at month 1 for each treatment arm separately (Table 4). These data show a highly significant trend over the 4 years of the trial toward lower absolute increments in both FEV1 and FVC in response to bronchodilator administration in each treatment group ($p < 0.0001$). This trend toward diminishing bronchodilator responsiveness over time could provide an explanation for the steeper post- versus pre-bronchodilator slope since it would result in relatively lower post-bronchodilator values in the later compared to the earlier years of the trial, as illustrated in Figure 3. It might also at least partially explain the comparatively larger differences in the slopes of the pre-vs. post-bronchodilator measurements in those with GOLD grades III and IV than I-II severity of airflow obstruction (Tables 3a-c) since the acute bronchodilator response (at least in terms of FEV1) tends to be more robust in those with moderate compared to those with severe/very severe airflow obstruction[11,12]. This trend toward smaller differences in the pre- vs. post-bronchodilator slopes in the UPLIFT participants with moderate airflow obstruction (average pre-bronchodilator FEV1 49 ± 8 [SD] % predicted) might also explain the absence of any discernible differences in the pre- vs. post-bronchodilator slopes in the Lung Health Study participants, who had only mild-to-moderate airflow obstruction with a mean baseline FEV1 of 78% predicted[2].

Since COPD is a progressive disease characterized by an accelerated age-related decline in lung function (1), the degree of airflow obstruction, on average, will worsen over time. Therefore, one explanation for the diminishing bronchodilator response over the course of the UPLIFT trial could be related to the impact of the progressively worsening severity of airflow obstruction itself on the bronchodilator response. Another possible explanation could be the development of tachyphylaxis to the acute bronchodilator effect of the albuterol that was administered along with ipratropium to elicit the post-bronchodilator FEV1 and FVC values at each measurement point. On the other hand, tolerance to the bronchodilator effect of a beta-agonist develops rapidly and appears to reach a plateau within 1-2 weeks of administration, after which it does not appear to progress further[13]. Moreover, tolerance to a beta-agonist is more evident as a decrease in the duration of action than in the peak

magnitude of bronchodilation[14]. Since the post-bronchodilator FEV1 in the UPLIFT trial was measured at the time of the *peak* response to the combination of albuterol and ipratropium, these findings suggest that bronchodilator tolerance does not explain the disparity in the rates of decline between the pre- versus the post-bronchodilator FEV1.

Whereas significant differences were noted in the pre- vs. post-bronchodilator slopes of lung function decline, the estimated variances of these slopes were similar. Therefore, no advantage accrues to post- over pre-bronchodilator spirometry with respect to reducing the variance of the slope of the FEV1 (or FVC) in the hope of increasing statistical power to demonstrate between-treatment differences in studies comparing different interventions on the rate of progression of COPD. While the known within- and between-day variability of bronchomotor tone[15] most likely contributes to the variability of the slope of FEV1 decline over time, bronchodilator administration has not been shown to abrogate the diurnal variability of airflow[16]. To the contrary, one might expect even greater variability in post- compared to pre-bronchodilator spirometry since responsiveness to bronchodilator administration has been shown to vary considerably from one session to the next[17-19]. On the other hand, prior self-administration of a bronchodilator during the washout period preceding spirometry test sessions in an intervention trial would have less of an impact on post- than pre-bronchodilator spirometric measurements.

It is of interest that post-hoc analyses of the results of the UPLIFT trial have revealed significant between-treatment (tiotropium vs. placebo) differences in the slope of the post-bronchodilator (but not the pre-bronchodilator) rate of decline in FEV1 in selected subgroups of trial participants, namely those with moderate airflow obstruction[20], maintenance-naïve subjects[21] and younger individuals (< 50 years of age)[22]. While the reasons for the apparently greater sensitivity of the post- compared to the pre-bronchodilator slope of FEV1 decline in detecting differences in treatment responses in selected subgroups of COPD patients is unclear, these findings suggest that the post-bronchodilator slope has utility in assessing treatment effects on rates of decline in lung function.

The strengths of this study include the large number of participants of varying severity in the UPLIFT trial, the relatively long follow-up period of 4 years, the use of centralized spirometry and rigorous quality control methods that resulted in high-quality measurements of FEV1 and FVC[23] and the use of relatively large doses of two different classes of bronchodilators with the timing of post-bronchodilator spirometry to correspond to the peak magnitude of bronchodilation from each agent, so that the post-bronchodilator measurements were likely to be near-maximal. On the other hand, the study had important limitations, particularly a high dropout rate (37% in the tiotropium arm and ∼45% in the placebo arm) that resulted in a large amount of missing data. While the mixed effects model assumes that the data are missing at random, it is clear that patient withdrawals were often due to worsening disease leading to missing data that cannot be assumed to be at random. Consequently, an additional analysis was performed in which the slope of decline in lung function was estimated using a joint analysis approach that models the joint distribution between the longitudinal outcome (FEV1 or FVC) and the patient dropout time[24] (supplemental Table 1E); this method reduces the estimated bias caused by premature discontinuations. In the joint analysis, the slopes estimated from the model adjusted for

covariates are slightly higher than those estimated from the mixed effects model, but the differences between the pre- and post-bronchodilator slopes determined from the two models are similar and remain highly significant ($p < 0.0001$).

Another potential limitation is that some patients may not have adhered strictly to the instructions to withhold their maintenance or rescue bronchodilator therapy for the protocol-defined interval prior to spirometry testing. If this occurred, it could have affected the pre-bronchodilator slope without influencing the slope derived from the post-bronchodilator measurements; however, unless this practice occurred systematically, it is unlikely to have affected the difference between the pre- and post-bronchodilator slopes.

In summary, in a population of COPD patients with moderate to very severe airflow obstruction followed for up to 4 years as part of the UPLIFT trial of tiotropium vs. placebo, we found significant differences in the slopes of the rates of decline in FEV1 and FVC determined from the post- vs. pre-bronchodilator measurements but no differences in the variances of these slopes. These pre- to post-bronchodilator slope differences tended to be larger in patients with severe and very severe airflow obstruction compared to those with moderate impairment. No differences in these findings were noted between the tiotropium and placebo treatment groups. The absolute improvements in FEV1 and FVC after bronchodilator administration diminished over the 4 years of the trial, providing a potential mechanism that might explain the steeper slopes determined from the post- compared to the pre-bronchodilator measurements. These slope differences need to be taken into account in studies of the impact of different interventions on the rate of decline in lung function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Partial support was received through a grant from the NIH/National Center for Advancing Translational Science (NCATS) UCLA CTSI Grant Number UL1TR000124. The authors also thank Boehringer-Ingelheim for providing the data from the UPLIFT trial; however, all analyses were carried out by the authors themselves independently of Boehringer-Ingelheim.

References

1. Tashkin DP, Wang HJ, Halpin D, et al. Comparison of the variability of the annual rates of change in FEV1 determined from serial measurements of the pre- versus post-bronchodilator FEV_1 over 5 years in mild to moderate COPD: Results of the Lung Health Study. Respiratory Research. 2012; 13:70. [PubMed: 22894725]
2. Anthonisen NR, Connett JE, Kiley JP, et al. for the Lung Health Study Research Group. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV_1. The Lung Health Study. JAMA. 1994; 272:1497–1505. [PubMed: 7966841]
3. Scanlon PD, Connett JE, Waller LA, et al. for the Lung Health Study Research Group. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease: the lung health study. Am J Respir Crit Care Med. 2000; 161:381–390. [PubMed: 10673175]
4. Pauwels RA, Lofdahl CG, Laitinen LA, et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. N Eng J Med. 1999; 340:1948–1953.

5. Burge PS, Calverley PMA, Jones PW, et al. Randomised, double-blind, placebo-controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ. 2000; 320:1297–1303. [PubMed: 10807619]
6. Vestbo J, Sorensen T, Lange P, et al. Long-term effect of inhaled budesonide im mild and moderate chronic obstructive pulmonary disease: a randomized controlled trial. Lancet. 1999; 353:1819–1823. [PubMed: 10359405]
7. The Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. N Engl J Med. 2000; 343:1902–1909. [PubMed: 11136260]
8. Decramer M, Rutten-van Molken M, Dekhuijzen PNR, et al. Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomized placebo-controlled trial. Lancet. 2005; 365:1552–1560. [PubMed: 15866309]
9. Tashkin DP, Celli B, Senn S, et al. for the UPLIFT study investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med. 2008; 359:1543–1554. [PubMed: 18836213]
10. Celli BR, Thomas NE, Anderson JA, et al. Effect of pharmacotherapy on rate of decline in lung function in chronic obstructive pulmonary disease. Results from the TORCH study. Am J Respir Crit Care Med. 2008; 178:332–338. [PubMed: 18511702]
11. Tashkin DP, Celli B, Decramer M, et al. Bronchodilator responsiveness in patients with COPD. Eur Respir J. 2008; 31:742–750. [PubMed: 18256071]
12. Celli B, Tashkin DP, Rennard SI, et al. Bronchodilator responsiveness and onset of effect with budesonide/formoterol pMDI in patients with COPD. Respir Med. 2011; 105:1176–88. [PubMed: 21531124]
13. Haney S, Hancox RJ. Rapid onset of tolerance to beta-agonist bronchodilation. Respir Med. 2005; 99:566–71. 99. [PubMed: 15823453]
14. Plummer AL. The development of drug tolerance to $beta_2$ adrenergic agents. Chest. 1978; 73:949–957. [PubMed: 28210]
15. Tashkin DP. Variations in FEV1 decline over time in COPD and its implications. Curr Opin Pulm Med. 2013; 19:116–124. [PubMed: 23287286]
16. Calverley PM, Lee A, Towse L, et al. Effect on tiotropium on circadian variation in airflow limitation in chronic obstructive pulmonary disease. Thorax. 2003; 58:855–60. [PubMed: 14514937]
17. Nisar M, Earis JE, Pearson MG, et al. Acute bronchodilator trials in chronic obstructive pulmonary disease. Am Rev Respir Dis. 1992; 146:555–9. [PubMed: 1387772]
18. Dorinsky PM, Reisner C, Ferguson GT, et al. The combination of ipratropium and albuterol optimizes pulmonary function reversibility testing in patients with COPD. Chest. 1999; 115:966–71. [PubMed: 10208193]
19. Calverley PM, Burge PS, Spencer S, et al. Bronchodilator reversibility testing in chronic obstructive pulmonary disease. Thorax. 2003; 58:659–64. [PubMed: 12885978]
20. Decramer M, Celli B, Kesten S, et al. for the UPLIFT investigators. Effects of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomized control trial. Lancet. 2009; 374:1171–8. [PubMed: 19716598]
21. Troosters T, Celli B, Lystig T, et al. on behalf of the UPLIFT investigators. Tiotropium as a first maintenance drug in COPD: A secondary analysis of the UPLIFT. Eur Respir J. 2010; 36:65–73. [PubMed: 20185426]
22. Morice AH, Celli B, Kesten S, et al. COPD in young patients: A pre-sepcified analysis of the four-year trial of tiotropium (UPLIFT). Respir Med. 2010; 104:1659–67. [PubMed: 20724131]
23. Janssens W, Liu Y, Liu D, Kesten S, et al. Quality and reproducibility of spirometry in patients with COPD: The UPLIFT® experience. Respir Med. 2013 May 25. Epub ahead of print. 10.1016/j.med.2013.04.015
24. Elashoff RM, Li G, Li N. A Joint Model for Longitudinal Measurements and Survival Data in the Presence of Multiple Failure Types. Biometrics. 2008; 64:762–771. [PubMed: 18162112]

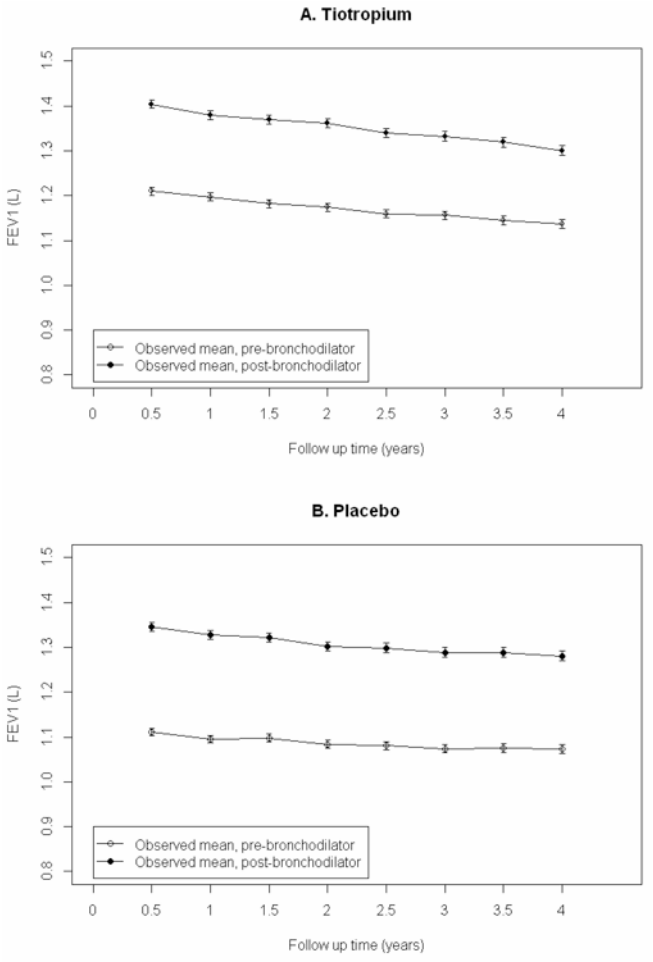

Figure 1.

Mean (± SE) observed values of pre- and post-bronchodilator FEV1 over 4 years in (A) the tiotropium group and (B) the placebo group.

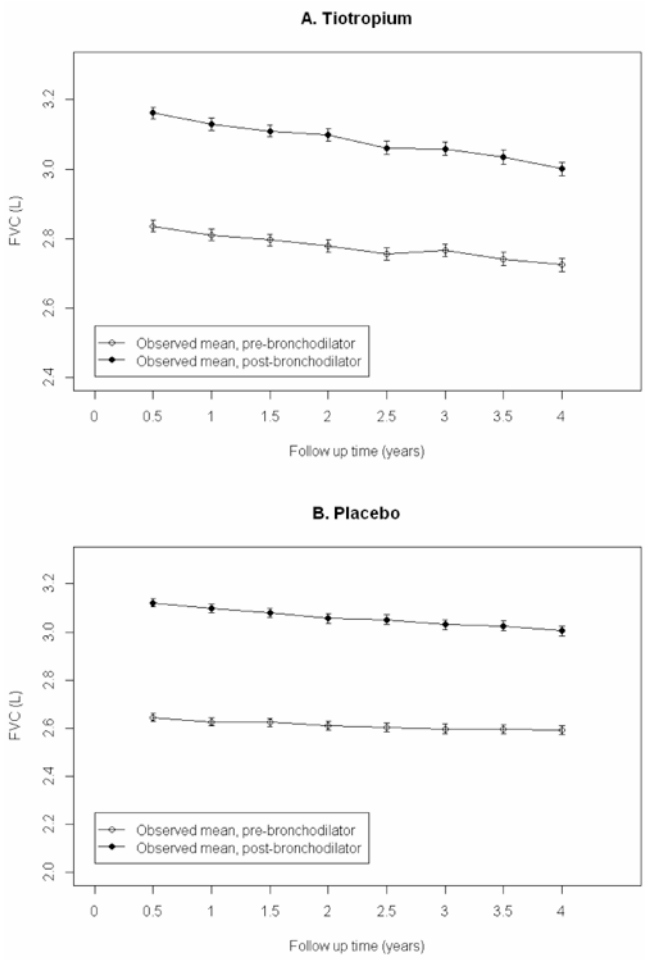

Figure 2.

Mean (± SE) observed values of pre- and post-bronchodilator FVC over 4 years in (A) the tiotropium group and (B) the placebo group.

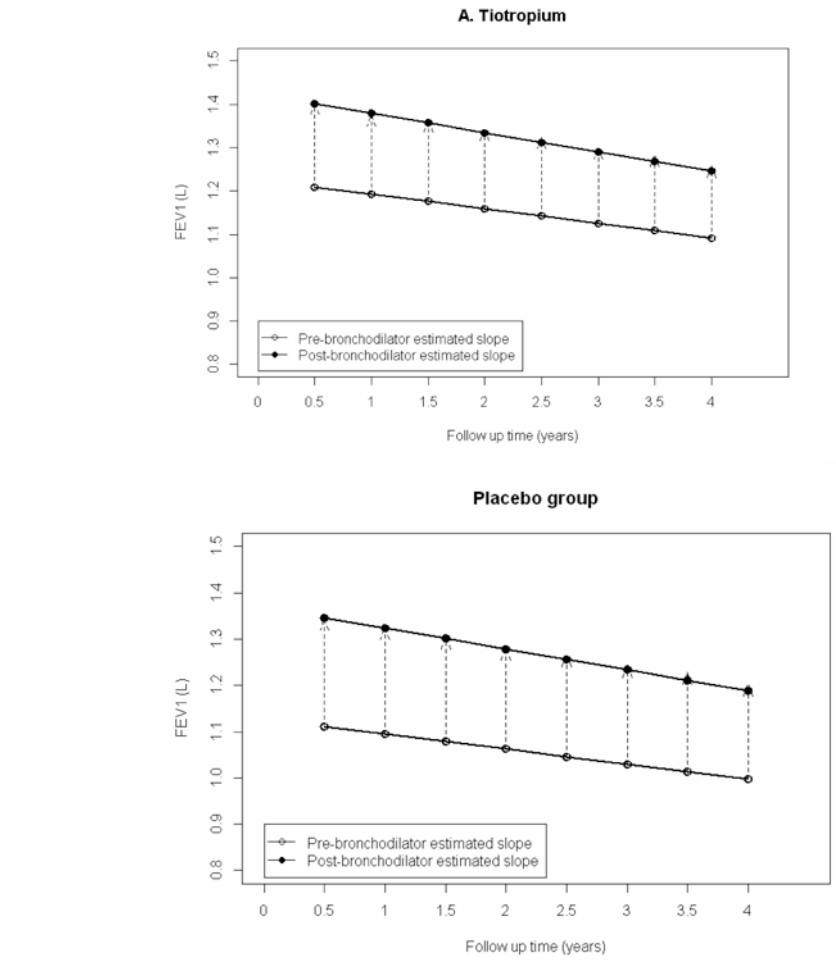

Figure 3.

Estimated slopes of annual decline in pre- and post-bronchodilator FEV1 in the tiotropium (A) and placebo (B) groups derived from the mixed effects model with adjustment for covariates over 4 years (solid lines) and the acute absolute increases in FEV1 (in ml) from the pre-bronchodilator value following bronchodilator administration at each time point except for the 1-month visit (dotted vertical arrows). The diminishing acute bronchodilator response over the 4 years of the trial appears to account for the steeper post-bronchodilator slope compared to the pre-bronchodilator slope.

Table 1

Baseline characteristics of subjects included in the analysis.

	Study Group		p-value
	Tiotropium	**Placebo**	
No. of Subjects	2578	2463	
Subject characteristics			
Gender (N, % Male)	1964, 76.2%	1850, 75.1%	0.38
Age, y (Mean ± SD)	64.3 ± 8.4	64.2 ± 8.4	0.63
Race (% White)	2323, 92.1%	2204, 91.6%	0.55
FEV_1, L – pre (Mean ± SD)	1.11 ± 0.4	1.12 ± 0.4	0.83
FEV_1, L– post (Mean ± SD)	1.35 ± 0.4	1.35 ± 0.4	0.98
FEV_1, % pred – pre (Mean ± SD)	39.8 ± 11.9	39.9 ± 11.8	0.64
FEV_1, % pred – post (Mean ± SD)	48.1 ± 12.5	48.2 ± 12.4	0.95
FVC, L – pre (Mean ± SD)	2.6 ± 0.8	2.7 ± 0.8	0.45
FVC, L – post (Mean ± SD)	3.1 ± 0.9	3.1 ± 0.9	0.52
FVC, % pred – pre (Mean ± SD)	74.8 ± 17.9	75.4 ± 18.0	0.23
FVC, % pred – post (Mean ± SD)	88.2 ± 18.6	88.7 ± 18.7	0.33
BMI, kg/ht^2 (Mean ± SD)	26.1 ± 5.0	26.0 ± 5.1	0.90
Smoking status (% current smokers)	745, 28.9%	722, 29.3%	0.75
Pack/Years (Mean ± SD)	48.9 ± 28.0	47.9 ± 27.9	0.17

Table 2

Linear slope estimates for the annual change in pre- and post-bronchodilator FEV_1 and FVC [a](ml/yr) both unadjusted and adjusted for covariates (height, gender, smoking status (see Methods), baseline % predicted FEV1 (or FVC), baseline acute % improvement) by intervention group. Linear mixed effects model approach.

Group	Unadjusted			Adjusted		
	Slope Estimate ml/yr	SE ml/yr	p	Slope Estimate ml/yr	SE ml/yr	p
FEV1						
Tiotropium (N=2578)						
Pre	-33.5	1.38		-33.5	1.37	
Post	-43.9	1.41		-44.1	1.42	
Δ	-10.4	1.26	<0.0001	-10.6	1.28	<0.0001
Placebo (N=2463)						
Pre	-32.6	1.40		-32.5	1.40	
Post	-45.1	1.45		-45.0	1.46	
Δ	-12.5	1.33	<0.0001	-12.5	1.36	<0.0001
FVC						
Tiotropium (N=2578)						
Pre	-47.0	2.82		-47.8	2.79	
Post	-65.0	2.81		-65.8	2.80	
Δ	-18.0	2.58	<0.0001	-18.0	2.63	<0.0001
Placebo (N=2463)						
Pre	-42.1	3.04		-41.8	2.99	
Post	-64.2	2.82		-63.6	2.84	
Δ	-22.1	2.92	<0.0001	-21.8	2.97	<0.0001

[a]for both FEV1 and FVC, data starting from 6 months on were included in the analysis.

Table 3

a. Linear slope estimates for the annual change in pre- and post-bronchodilator FEV_1 and FVC [a](ml/yr) both unadjusted and adjusted for covariates (height, gender, smoking status, baseline % predicted FEV1 (or FVC), baseline acute % improvement) by intervention group. Linear mixed effects model approach. **GOLD stage I and II.**

Group	Unadjusted			Adjusted		
	Slope Estimate ml/yr	SE ml/yr	p	Slope Estimate ml/yr	SE ml/yr	p
FEV1						
Tiotropium (N=1227)						
Pre	-37.4	2.09		-37.1	2.07	
Post	-46.1	2.14		-46.2	2.13	
Δ	-8.7	1.95	<0.0001	-9.1	1.98	<0.0001
Placebo (N=1179)						
Pre	-39.1	2.13		-38.9	2.13	
Post	-50.9	2.15		-50.6	2.16	
Δ	-11.8	2.03	<0.0001	-11.7	2.05	<0.0001
FVC						
Tiotropium (N=1227)						
Pre	-44.7	3.64		-44.0	3.56	
Post	-53.3	3.55		-52.8	3.49	
Δ	-8.6	3.48	0.0135	-8.8	3.54	0.0129
Placebo (N=1179)						
Pre	-45.6	4.04		-45.1	3.92	
Post	-60.7	3.76		-60.2	3.70	
Δ	-15.1	3.97	0.0001	-15.1	4.01	0.0002

[a] for both FEV1 and FVC, data at **6 months** or later were included in the analysis.

Table 3b. Linear slope estimates for the annual change in pre- and post-bronchodilator FEV_1 and FVC[a] (ml/yr) both unadjusted and adjusted for covariates (height, gender, smoking status[b], baseline % predicted FEV1 (or FVC), baseline acute % improvement) by intervention group. Linear mixed effects model approach. GOLD stage III.

Group	Unadjusted			Adjusted		
	Slope Estimate ml/yr	SE ml/yr	p	Slope Estimate ml/yr	SE ml/yr	p
FEV1						
Tiotropium (N=1117)						
Pre	-30.7	1.97		-30.7	1.95	
Post	-42.7	2.04		-42.8	2.05	
Δ	-12.0	1.74	<0.0001	-12.1	1.75	<0.0001
Placebo (N=1060)						
Pre	-27.3	1.95		-27.2	1.94	
Post	-40.5	2.12		-40.3	2.12	
Δ	-13.2	1.87	<0.0001	-13.1	1.89	<0.0001
FVC						

Table 3b. Linear slope estimates for the annual change in pre- and post-bronchodilator FEV_1 and FVC[a] (ml/yr) both unadjusted and adjusted for covariates (height, gender, smoking status[b], baseline % predicted FEV1 (or FVC), baseline acute % improvement) by intervention group. Linear mixed effects model approach. GOLD stage III.

Group	Unadjusted			Adjusted		
	Slope Estimate ml/yr	SE ml/yr	p	Slope Estimate ml/yr	SE ml/yr	p
Tiotropium (N=1117)						
Pre	-50.2	4.58		-49.8	4.59	
Post	-76.7	4.68		-76.3	4.69	
Δ	-26.5	4.09	<0.0001	-26.5	4.12	<0.0001
Placebo (N=1060)						
Pre	-41.0	4.94		-40.9	4.85	
Post	-67.0	4.64		-66.7	4.67	
Δ	-26.0	4.64	<0.0001	-25.8	4.70	<0.0001

[a] for both FEV1 and FVC, data at **6 months** or later were included in the analysis.

Table 3c. Linear slope estimates for the annual change in pre- and post-bronchodilator FEV_1 and FVC[a] (ml/yr) both unadjusted and adjusted for covariates (height, gender, smoking status[b], baseline % predicted FEV1 or FVC, baseline acute % improvement) by intervention group. Linear mixed effects model approach. GOLD stage IV.

Group	Unadjusted			Adjusted		
	Slope Estimate ml/yr	SE ml/yr	p	Slope Estimate ml/yr	SE ml/yr	p
FEV1						
Tiotropium (N=197)						
Pre	-23.7	3.56		-24.2	3.64	
Post	-35.9	4.10		-36.9	4.32	
Δ	-12.2	3.86	0.0016	-12.7	3.93	0.0012
Placebo (N=188)						
Pre	-13.4	3.48		-14.3	3.40	
Post	-28.5	3.60		-28.8	3.63	
Δ	-15.1	3.80	<0.0001	-14.5	3.83	0.0002
FVC						
Tiotropium (N=197)						
Pre	-60.7	11.6		-64.5	11.7	
Post	-89.7	11.2		-95.7	11.7	
Δ	-29.0	11.0	0.0084	-31.2	11.2	0.0053
Placebo (N=188)						
Pre	-17.7	12.6		-19.8	12.8	
Post	-71.8	11.0		-72.1	11.8	
Δ	-54.1	12.7	<0.0001	-52.3	12.8	<0.0001

[a] for both FEV1 and FVC, data at **6 months** or later were included in the analysis.

Table 4

Absolute change in milliliters (mean ± SD) in FEV_1 and FVC comparing post- versus pre-bronchodilator measurements at each time point over 4 years

Time	FEV_1		FVC	
	Tiotropium	Placebo	Tiotropium	Placebo
1.0m	197 ± 159	235 ± 171	347 ± 364	486 ± 409
0.5y	195 ± 159	235 ± 168	328 ± 336	480 ± 398
1.0y	183 ± 153	231 ± 165	319 ± 335	470 ± 391
1.5y	187 ± 157	226 ± 165	312 ± 334	456 ± 392
2.0y	184 ± 149	219 ± 157	314 ± 330	448 ± 372
2.5y	182 ± 150	221 ± 159	306 ± 327	451 ± 389
3.0y	175 ± 153	214 ± 154	290 ± 322	430 ± 375
3.5y	175 ± 147	215 ± 156	291 ± 319	431 ± 384
4.0y	166 ± 143	206 ± 151	278 ± 304	408 ± 369
p-value for trend	<0.0001	<0.0001	<0.0001	<0.0001