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BRONCHODILATOR RESPONSIVENESS IN PATIENTS WITH COPD

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DISCLOSURES

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ABSTRACT

Background: The degree of acute improvement in spirometric indices after bronchodilator inhalation varies among COPD patients and depends on the type, dose and timing of bronchodilator administered.

Methods: We examined acute bronchodilator responsiveness at baseline in a large cohort of patients with moderate to very severe COPD participating in UPLIFT, a 4-year, randomized, double-blind trial evaluating the efficacy of tiotropium 18 mcg daily in reducing the rate of decline in lung function. After washout of respiratory medications, patients received 80 mcg ipratropium followed by 400 mcg albuterol. Spirometry was performed before and 90 minutes following ipratropium. Criteria used for FEV_1 responsiveness: ≥12% and 200 ml, ≥15% increase over baseline, and ≥10% absolute increase in percent predicted.

Results: 5,756 patients had data meeting criteria for analysis. Age=64.5 years; males=75%. Baseline FEV_1=1.10 L (39.3% predicted) and FVC=2.63 L. Compared with baseline, mean improvements in FEV_1=229 ml, FVC=407 ml. 53.9% of patients had 12% and 200 ml improvements in FEV_1; 65.6% had ≥15% improvement in FEV_1; and 38.6% had ≥10% absolute increase in FEV_1 percent predicted.

Conclusion: The majority of patients with moderate to very severe COPD demonstrate meaningful increases in lung function following administration of an inhaled anticholinergic plus sympathomimetic bronchodilators.

INTRODUCTION

Acute bronchodilator responsiveness in patients with chronic obstructive pulmonary disease (COPD) has not been rigorously well characterized in large cohorts. This is because determination of the response to a bronchodilator is influenced by physiological and methodological factors, including differences in baseline degree of airflow obstruction, diurnal and day-to-day variability in bronchomotor tone, dose and class of inhaled bronchodilator therapy, method of bronchodilator administration (e.g., metered dose inhaler with or without a spacer or solution nebulizer), dose of the bronchodilator, timing of post-bronchodilator spirometry [1] and wash-out of maintenance respiratory medications. To add further complexity, repeated testing has shown considerable intra-individual variability in acute bronchodilator responsiveness in COPD [2,3].

The Global Initiative for Obstructive Lung Disease (GOLD) and the American Thoracic Society/European Respiratory Society (ATS/ERS) COPD guidelines define COPD as a preventable and treatable disease characterized by airflow limitation that is partially reversible [4, 5]. Nevertheless, patients with COPD are still commonly thought to have diminished acute bronchodilator responsiveness compared with asthmatics, and reversibility testing is still sometimes proposed as a method of discriminating between asthma and COPD, despite evidence to the contrary [6].

The Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) trial is a large-scale, 4-year, multinational clinical trial evaluating whether maintenance treatment with tiotropium 18 mcg once daily is associated with a decrease in the rate of decline of FEV_1 over time in patients with COPD [7]. In this study, baseline spirometry was performed before

and following administration of the short-acting bronchodilators, ipratropium bromide and albuterol, timed to achieve maximal or near maximal bronchodilation [3]. The baseline post-bronchodilator FEV_1 values in the UPLIFT study provided a unique opportunity to 1) examine acute bronchodilator responsiveness in a large cohort of patients with moderate to very severe COPD, 2) to determine the proportion of this population that would be considered "responsive" or "non-responsive" using various reversibility criteria, and 3) to explore determinants of responsiveness by examining the characteristics of patients who met and did not meet specific responsiveness criteria.

METHODS

Study Design

The UPLIFT trial is a randomized, double-blind, placebo-controlled, parallel-group clinical trial examining the effect of tiotropium 18 mcg daily on the rate of decline in FEV_1 over 4 years in patients with COPD [7]. The present analysis examines bronchodilator responsiveness using blinded, aggregate baseline data obtained from all patients who had values available for both pre- and post-bronchodilator FEV_1.

The protocol was approved by ethics committees and/or institutional review boards for all participating centers. Written, informed consent was obtained from all patients participating in the study.

Participants

Patients were recruited from 475 investigational centers in 37 countries. Patients were eligible for inclusion if they had a diagnosis of COPD, were ≥40 years of age, had a smoking history of ≥10 pack years and both a post-bronchodilator FEV_1 ≤70% of predicted and an FEV_1/FVC <0.70 in response to near-maximal doses of both salbutamol and ipratropium bromide. Patients were excluded if they had a respiratory infection or an exacerbation of COPD in the 4 weeks prior to screening, had a history of asthma or pulmonary resection, used supplemental oxygen >12 hours per day, or had a significant disease other than COPD which, in the opinion of the investigator, might influence the results of the study or the patient's ability to participate in the study. Patients were permitted to continue using all previously prescribed respiratory medications other than inhaled anticholinergics provided the prescriptions had not

changed in the 6 weeks prior to randomization. Details of the trial design have been published [6].

Procedures

At Visit 1, baseline data including demographics, smoking status, use of concomitant therapies, and other relevant medical history were obtained and initial screening spirometry was performed after administration of salbutamol 200 mcg. Patients who demonstrated a post-albuterol FEV_1 ≤70% of predicted and FEV_1/FVC <0.70 at Visit 1 were eligible to continue. These patients returned to the study center 2 weeks later (Visit 2) to perform pre- and post-bronchodilator spirometry (baseline).

Prior to baseline pulmonary function testing at Visit 2, patients were asked to adhere to medication washout requirements which included withholding short-acting and long-acting β-agonists (for ≥8 and ≥12 hours, respectively), short-acting and long-acting theophylline preparations (for ≥24 and ≥48 hours, respectively), and antileukotrienes (for ≥ 48 hours) prior to spirometry. Patients were discouraged from smoking during the study visit and were not permitted to smoke within 30 minutes of spirometry. We relied on subjects' self-report regarding their adherence to these restrictions, as done routinely in clinical trials.

At Visit 2, pre-bronchodilator spirometry was performed and then patients received 4 inhalations of ipratropium (80 mcg via metered dose inhaler) followed 60 minutes later by 4 inhalations of salbutamol (400 mcg via metered dose inhaler) to ensure maximum or near-maximum bronchodilation (Figure 1). A spacer was not used. Post-bronchodilator spirometry was measured 30 minutes after inhalation of the salbutamol. Spirometry was deemed acceptable if ATS criteria were met [8]. Manoeuvres were performed in triplicate and the best of three

efforts, defined as the highest acceptable FEV_1 and the highest acceptable FVC obtained on any of three manoeuvres (even if not from the same curve), constituted the data for that test set [8].

To minimize variability, all sites were provided with identical spirometry systems (KoKo Spirometer, Quantum Research, Inc., Louisville, CO, USA) including customized, study-specific software, and the study staff received standardized training at the investigator meetings. All technicians were required to meet proficiency requirements in the use of the equipment and demonstrate the ability to perform technically acceptable pulmonary function tests by ATS criteria prior to testing study patients [8]. During testing, the spirometry software provided immediate feedback to the technician regarding acceptability and reproducibility of FVC efforts. Following test completion, spirometric measurements were electronically transmitted for centralized quality review (nSpire Health Inc, Louisville, CO, USA) per ATS recommendations. Feedback was provided to centers on a regular basis to maintain quality over time [6,8].

Statistical analysis

Data from all randomized patients with moderate to very severe COPD who performed technically acceptable pre- and post-bronchodilator pulmonary function testing at baseline were included in the analysis. Data from patients with mild COPD (n=3) and those without technically acceptable pre- and post-bronchodilator measurements (n = 233, 3.9% of patients) were excluded from the present analysis.

FEV_1 responsiveness was assessed using three different published criteria: ≥12% and 200 ml [8,9,10], ≥15% increase over baseline [11,12)], and ≥10% absolute increase in percent predicted [2,13,14]. To further examine bronchodilator responsiveness and the influence of baseline severity of airflow limitation, FEV_1 and FVC improvements above baseline were

stratified according to GOLD Stage using the criteria of $\geq$12% and 200 ml, and $\geq$15% increase over baseline. The cohort was analysed for the proportion of patients achieving these pre-defined increases in FEV_1 and FVC according to the following: (a) FEV_1 response with or without an FVC response, (b) FVC response with or without an FEV_1 response, (c) FEV_1 without an FVC response, (d) FVC response without an FEV_1 response, (e) either an FEV_1 or FVC response, and (f) both an FEV_1 and FVC response. The results are displayed for descriptive purposes and not statistically analyzed due to the smaller individual groupings.

The characteristics of patients with and without bronchodilator responsiveness who met and did not meet these criteria were summarized descriptively, and p-values were computed using Student's t-tests. Frequency distributions of bronchodilator responses according to percentage and absolute milliliter increases in FEV_1 were generated. Multivariate logistic regression with covariates including gender, smoking status, age, self reported smoking pack years, COPD duration, baseline pre-bronchodilator FEV_1 (% predicted) and SGRQ total score, was used to analyze the association between baseline characteristics and the presence or absence of acute bronchodilator responses according to each of the three criteria used. A step-wise model selection procedure was used to identify the statistically significant variables.

RESULTS

Study population

A total of 8,019 patients were screened for participation in the study over 14 months. Of these, 5,993 patients met eligibility criteria and were randomized into the UPLIFT study. Technically acceptable baseline pre- and post-bronchodilator pulmonary function data were available on 5,756 moderate to very severe COPD patients. Results presented here are for this cohort. Demographics and baseline characteristics and baseline use of respiratory medications are displayed in Table 1.

Bronchodilator Responsiveness

Mean pre-bronchodilator FEV_1 and FVC were 1.10 L and 2.63 L, respectively (Figure 1). Following bronchodilator administration, there was a 229 ml (23.4%) mean increase in FEV_1 and a 471 ml (20.1%) mean increase in FVC ($p<0.001$ vs. pre-bronchodilator, Figure 1). This improvement corresponded to an increase in FEV_1 percent of predicted from 39.3% to 47.6%, an absolute increase of 8.3%.

To examine responsiveness, the distributions of the post-bronchodilator percent and absolute improvements in FEV_1 and the absolute improvements in FEV_1 percent of predicted are shown in Figure 23. Overall, there were substantial improvements in FEV_1 but the percentage of patients who could be characterized as "responsive" differed depending on the criterion applied. In the cohort under study, 65.6% met the criterion of a ≥15% increase in FEV_1 (Figure 3A); 53.9% met the criterion for an increase in FEV_1 of both ≥12% and 200 mL (73% of patients had an increase of ≥12% [Figure 2A] and 55% had ≥200 mL [Figure 2B]); and 38.6% were

characterized as reversible based on a ≥10% absolute improvement in FEV_1 percent of predicted (Figure 2C). If we define "paradoxical bronchospasm" as a decrease in FEV1 by ≥12% and ≥200 ml, only a minute fraction (0.24%) of the subjects demonstrated this phenomenon.

Characteristics Associated with Bronchodilator Responsiveness

The baseline characteristics, baseline lung function, and COPD severity of patients who met or did not meet each of the three responsiveness criteria are shown in Tables 2 and 3, respectively. Certain characteristics of responsive relative to poorly responsive patients varied depending upon the criteria used. The statistically significant variables from the multivariate logistic regression model are displayed in Table 4. The odds for women tends to be higher than for men on meeting the criteria of a ≥15% improvement in FEV_1 ($p<0.0001$) or a ≥10% absolute increase in FEV_1 percent of predicted ($p<0.0001$); whereas, the odds for men meeting the ≥12% and 200 mL threshold ($p<0.0001$) is higher than for women. Age was a significant factor only for the criterion of a ≥12% and 200 mL: a patient of older age tends to have a smaller odds of being responsive under this criterion. A higher percentage of active smokers were poorly responsive using the criteria of ≥15% FEV_1, but did not show statistical significance in the multivariate logistic regression model. Interestingly, the mean number of self-reported pack years of cigarette use was lower, the duration of COPD was numerically longer, and the SGRQ total score was consistently higher in poorly responsive patients regardless of which criterion was applied. The logistic regression model shows that higher odds of responsiveness is associated with lower number of pack years ($p<0.001$, $p=0.014$, $p=0.006$ for criteria ≥12% and 200 mL, ≥15% improvement in FEV_1, and ≥10% absolute increase in FEV_1, respectively) and better

SGRQ total score (i.e., lower scores) ($p<0.0001$ for all criteria). However, the duration of COPD did not show statistical significance in the logistic regression in all cases.

As expected, the degree of improvement in FEV1 was significantly greater in responsive compared to poorly responsive subjects for all three threshold criteria. Interestingly, however, statistically significant improvements were observed in mean FEV_1 after the administration of bronchodilators in the poorly responsive, as well as the responsive, group regardless of threshold criteria, a finding facilitated by the large number of subjects studied . The mean baseline pre-bronchodilator FEV_1 percent of predicted was higher in the poorly-responsive patients compared to responsive patients for all criteria (Table 3). However, the degree of difference in baseline FEV_1 percent of predicted between responsive and poorly responsive patients was greater using the criterion of a change in FEV_1 ≥15% (36.3% vs 45.2% predicted, $p <0.001$) compared with the criteria of a change in FEV_1 ≥12% and 200 mL (38.5% vs 40.3% predicted, $p <0.001$) or a change in absolute FEV_1 percent of predicted of ≥10% (38.8% vs 39.7% predicted, $p=0.003$). When patients were characterized by COPD severity within each reversibility criterion, a markedly higher percentage of Stage IV patients were poorly-responsive than responsive for the reversibility criteria of change in FEV_1 ≥12% and 200 mL and change in absolute FEV_1 % predicted ≥10% (Table 3).

Bronchodilator responsiveness according to GOLD stage and consideration of whether flow (FEV1) and volume (FVC) responses occur together or can occur without the other are illustrated in Figure 3. The figure displays the proportion of patients in GOLD Stages II, III and IV achieving pre-defined criteria for responsiveness; GOLD Stage I is not displayed since there were too few patients in this stage to provide meaningful data. The percentage of COPD patients exhibiting a flow response by the ATS criteria of ≥12% and ≥200 ml decreased progressively

with increasing disease severity, whereas the percentages of those with a flow response by the ≥15% criterion or a volume response by either of the two responsiveness criteria was relatively little affected by GOLD stage (Figure 3A). The percentage of COPD patients who exhibited a volume response without a significant flow response (Figure 3B) varied from 5 to 49% depending on the criteria and GOLD stage. The percentage of patients exhibiting volume responses without flow responses increased with the severity of airflow obstruction, particularly for the ATS criteria. If either FEV_1 or FVC response was considered (Figure 3C), approximately 70% of patients exhibited a significant response irregardless of GOLD stage.

DISCUSSION

The most important finding in this study of a large cohort of patients with severe and very severe COPD is that the magnitude of bronchodilator responsiveness is larger than expected. In addition, the prevalence of "significant" responses varies according to the criteria used. Until recently, COPD had been characterized as a disease with largely irreversible airflow obstruction. Methodological issues (class and dose of acute bronchodilators, timing of post-bronchodilator spirometry following bronchodilator administration; suboptimal inhaler technique; insufficient washout period to minimize residual effects of previous bronchodilator therapy) [1], as well as criteria for responsiveness may have resulted in misclassification of reversibility. Although it is now widely accepted that COPD is characterized by partially reversible airflow obstruction, the degree of acute responsiveness to bronchodilators in general use for COPD has not been rigorously analyzed. The UPLIFT trial provided the opportunity to investigate the degree of acute responsiveness to large doses of two different classes of inhaled bronchodilators in a large cohort of patients with moderate to very severe COPD.

Following administration of ipratropium and albuterol timed to achieve maximal or near-maximal bronchodilation, the majority of COPD patients achieved significant improvements in FEV_1 over pre-bronchodilator values (23.4% increase from pre- to post-bronchodilator values). Up to 65.6% of patients met at least one common criterion for FEV_1 responsiveness after acute administration of bronchodilators. However, when the three criteria (12% and 200 mL, ≥15%, or ≥10% absolute increase in the percentage of predicted) were evaluated independently, the percentage of patients considered to have reversible airflow obstruction differed substantially (53.9% vs. 65.6% vs. 38.6%, respectively). Women were less likely to exhibit responsiveness to

bronchodilators than men using a percent and an absolute volume improvement (i.e. ≥12% and ≥200 ml above baseline) for response but more likely than men by using a percent or percent predicted improvement alone. Lower values for pre-bronchodilator FEV_1 % predicted were also associated with a greater likelihood of a positive bronchodilator response for all three criteria, although the association was strongest for the criterion based on >15% improvement over the baseline FEV_1, which is most influenced by the baseline value. The biasing influence of the baseline value can be obviated to some extent either by including an absolute level of improvement in FEV_1 in the criterion for a positive response or by expressing the response in terms of an absolute improvement in the percent predicted FEV_1.

Selection of bronchodilator class, as well as dose and timing, may affect the degree of responsiveness observed in a study population. While responses to β-agonists are frequently used to characterize bronchodilator responsiveness in asthma, COPD patients may manifest more pronounced improvements after administration of anticholinergics [15]. Timing of spirometry to coincide with the expected time to peak bronchodilation assures that the optimal response to a bronchodilator is captured. Time-response curves for short-acting beta-agonists and cholinergic antagonists have demonstrated peak responses to these two classes of bronchodilators at approximately 30-60 and 60-90 minutes, respectively [1]. As already noted, combining bronchodilators with different mechanisms of action may increase the maximum degree of bronchodilation achievable with either drug alone [16].

In the UPLIFT trial, therefore, the administration of double the standard doses of both albuterol and ipratropium, the withholding of previous bronchodilator agents for periods exceeding their known duration of action (to avoid confounding by residual effects of previous bronchodilator therapy), the performance of post-bronchodilator spirometry at the expected time

of peak or near-peak bronchodilation of each of the two agents (30 minutes after albuterol and 90 minutes after ipratropium) and the use of centralized spirometry with rigorous quality control provide the best opportunity to determine the optimal bronchodilator responsiveness in patients with COPD.

Even when using methodologically optimized bronchodilator testing, as in UPLIFT, the threshold criteria selected to define responsiveness may themselves further confound the assessment. There is no complete agreement on the recommended criteria for judging a short-term response to a bronchodilator to be "significant", partly because of the lack of consensus concerning how the bronchodilator response should be expressed [8,17]. Currently, the three most widely used methods of expressing the response to a bronchodilator are: ≥15% improvement over the pre-bronchodilator FEV_1 [11]; ≥12% improvement plus an absolute volume increase of 200 ml over the pre-bronchodilator FEV_1 [8,9]; and an improvement over the pre-bronchodilator FEV_1 of ≥10% of the predicted value [2,13,14]. While the selection of these recommended criteria is somewhat arbitrary, the rationale for the 12-15% improvement over the pre-bronchodilator value is supported by some evidence indicating that these thresholds exceed normal within-trial variability [18] and responses to placebo inhalation [19], at least in asthmatic subjects. A low denominator (i.e., a low pre-bronchodilator FEV_1) can magnify the response when expressed as a percent above baseline; however, the ATS criteria include the requirement of an additional increment in absolute volume (200 ml) that would offset the influence of the pre-bronchodilator FEV_1 on the percentage improvement [8] and take into consideration the limits of measurement reproducibility. On the other hand, a pre-specified absolute increase in FEV_1 tends to minimize what may be clinically meaningful improvements in patients with very severe COPD, who may experience perceptible benefit from relatively modest absolute improvements

in FEV_1 above a very low baseline value. The criterion of a 10% improvement in the percent predicted FEV_1 represents another strategy for minimizing the influence of a low denominator [2,14,20] and, in one study of patients with obstructive airways disease, proved to be the most useful method of expressing the bronchodilator response [14].

In the present study, we demonstrate that the application of different criteria to post-bronchodilator improvements in FEV_1 results in differing prevalence of responsiveness. Patients may manifest post-bronchodilator improvements in airflow which meet one of these criteria, but may not meet all three. Hence, classifications of responsiveness (i.e. "responsive" vs. "not responsive") are dependent on the criteria applied. In addition, we noted that statistically significant improvements in FEV_1 were observed after administration of bronchodilators in both "responsive" and "poorly responsive" subgroups, regardless of which criteria were applied, indicating that each method of expressing reversibility is a continuous variable and underscoring the importance of distinguishing between statistically significant and clinically meaningful changes. Dichotomization into absolute terms of "responsive" and "not responsive" may not be clinically useful in the management of patients with COPD.

Some baseline characteristics of the patient population appear to be associated with such classifications of responsiveness. Men appeared to be more often responsive than women on certain responsiveness criteria. A higher percentage of active than former smokers were not reversible using the criterion of ≥15% FEV_1. Poorly responsive patients generally had lower self-reported pack years of cigarette use, a longer duration of COPD, and a higher SGRQ total score regardless of which criterion was applied. However, these apparent associations should be viewed with caution given the wide range of values and inherent biases (e.g. women have smaller lung volumes than men, ex-smokers may have lower lung function than current smokers

who can more readily tolerate continued smoking), which may not necessarily be adequately adjusted for in the multivariate analysis.

While the purpose of this report was to assess bronchodilator responsiveness in COPD as commonly defined by published criteria for changes in FEV_1 (2,8-14), it has long been recognized that a large proportion of COPD patients who fail to exhibit the requisite threshold increase in FEV_1 according to one or more of these criteria nonetheless demonstrate a substantial post-bronchodilator improvement in FVC or VC, which can be considered an "isolated volume response" [1,21]. Newton et al. reported substantial increases in FVC following salbutamol (336 and 204 ml in severely and moderately hyperinflated COPD patients, respectively), as well as parallel improvements in inspiratory capacity and reductions in functional residual capacity and residual volume, despite significant improvements in FEV_1 in only a minority of the patients [22]. The clinical significance of these changes in lung volumes has been underscored by the observation that improvements in exercise endurance and dyspnea during exercise following bronchodilator therapy are correlated better with increases in inspiratory capacity than with increases in FEV_1 [23]. In the present study, mean FVC improved by 20.1% and 471 ml over baseline, consistent with these earlier observations. It is also noteworthy that as many as 49% of the patients with very severe COPD showed a volume response without a flow response to the bronchodilators, when the ≥12% and 200 ml increase over baseline criterion was applied to both FEV_1 and FVC, and that the percentage of patients with an isolated volume response increased with the severity of airflow obstruction (Figure 3). At the present time, however, bronchodilator responsiveness is formally defined only by improvements in FEV_1, although a compelling argument could be made for re-defining bronchodilator responsiveness to include improvement not only in FEV_1 but also in lung volumes alone and in addition to increases in FEV_1, especially

in COPD patients, who are more likely to exhibit an isolated volume response than patients with asthma.

In summary, the results reported here in 5,756 COPD patients confirm and extend previous reports of substantial acute bronchodilator reversibility in patients with COPD who had no other features of asthma, regardless of the method used to define reversibility. Findings indicated that, at study entry, patients with moderate to very severe COPD participating in the global clinical trial UPLIFT were responsive to near-maximal doses of two different classes of inhaled bronchodilators as evidenced by increases over baseline in FEV_1 and FEV_1 percent of predicted. Over one-half to nearly two-thirds of the subjects met the most commonly used criteria for acute bronchodilator responsiveness and more than one-third showed acute responsiveness by the increase in percent predicted criterion. It should not be surprising that the effect of baseline characteristics on responsiveness varies depending on the criterion used for defining reversibility. In the present study, it was also demonstrated that patients with COPD can exhibit a volume response to short-acting bronchodilators without a significant flow response and that the proportion of patients exhibiting volume responses without flow responses increases with the severity of airflow obstruction. The major conclusion from the present study is that the method of assessing near-maximal bronchodilator responsiveness used in UPLIFT, although difficult to implement in clinical practice, shows more reversibility in COPD patients than has generally been thought and can be used in research.

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Table 1. Demographics and baseline characteristics of analysis cohort. Data are presented as mean (SD) or percent of population.

Characteristic	**Data for analysis cohort N=5,756**
Age (years)	64.5 (8.5)
Male (%)	74.6
Race (%)	
White	90
Asian	6.3
Black	1.6
Not available	2.0
Current smoker (%)	30.6
Smoking history (pack-years)	48.7 (27.9)
Duration of COPD (years)	9.8 (8.3)
BMI (kg/m^2)	26.0 (5.1)
SGRQ total score	45.9 (17.1)
Pre bronchodilator FEV_1 (% predicted)	39.3 (12.0)
Post bronchodilator FEV_1 (% predicted)	47.6 (12.6)
GOLD Stage (%)	
Stage II: Moderate	46.6
Stage III: Severe	44.7
Stage IV: Very severe	8.8
Medication Use	

Any respiratory medication	93.1
Short-acting β-agonists	68.5
Any long-acting bronchodilator	60.5
Inhaled steroids	61.4
Short-acting inhaled anticholinergics	44.5
Xanthines	28.6
Oxygen	2.0

Table 2. Patient

characteristics according to bronchodilator responsiveness at baseline.

	ΔFEV$_1$ ≥12% and ≥200 ml		**ΔFEV$_1$ ≥15%**		**Δabsolute FEV$_1$ % predicted ≥10%**	
	Responsive	**Poorly Responsive**	**Responsive**	**Poorly Responsive**	**Responsive**	**Poorly Responsive**
Number of patients (% of total)	3103 (53.9)	2653 (46.1)	3776 (65.6)	1980 (34.4)	2224 (38.6)	3532 (61.4)
Age (years)*	64.0 (8.4)§	65.1 (8.4)	64.5 (8.5)	64.4 (8.5)	64.5 (8.6)	64.5 (8.4)
Male (%)	79.2§	69.2	73.8†	76.3	72.6	75.9
BMI*	26.1 (5.0)†	25.7 (5.2)	25.8 (5.0)§	26.3 (5.2)	26.1 (5.0)	25.9 (5.1)
Current smoker (%)	30.7	30.5	28.9‡	33.8	30.4	30.7
Smoking history (pack-years)*	50.0 (28.9)§	47.1 (26.5)	49.4 (28.3)†	47.3 (27.0)	49.6 (28.9)†	48.1 (27.2)
Duration of COPD (years)	9.7 (7.4)	10.0 (7.9)	9.8 (7.6)	9.9 (7.9)	9.6 (7.3)	9.9 (7.9)
SGRQ total score*	44.4 (16.8)§	47.7 (17.3)	45.8 (16.7)	46.1 (17.7)	44.0 (16.8)§	47.1 (17.2)

*Mean (SD) $^{\dagger}p<0.05$; $^{\ddagger}p<0.001$; $^{\S}p<0.0001$ comparing responsive vs. poorly responsive

Table 3. Baseline spirometry and severity of COPD according to bronchodilator responsiveness at baseline

	ΔFEV$_1$ ≥12% and ≥200 mL		**ΔFEV$_1$ ≥15%**		**Δabsolute FEV$_1$ % predicted ≥10%**	
	Responsive	**Poorly Responsive**	**Responsive**	**Poorly Responsive**	**Responsive**	**Poorly Responsive**
Pre bronchodilator FEV$_1$ (% predicted)*	38.5 (10.5) §	40.3 (13.4)	36.3 (10.6) §	45.2 (12.2)	38.8 (10.0) †	39.7 (13.0)
Post bronchodilator FEV$_1$ (% predicted)*	50.6 (11.20) §	44.0 (13.3)	47.4 (12.4)	47.9 (13.1)	52.6 (10.3) §	44.4 (13.0)
GOLD Stage	§		‡		§	
Stage II: Moderate (%)	56.0	35.4	45.7	48.1	62.7	36.3
Stage III: Severe (%)	40.6	49.5	45.9	42.5	36.0	50.2
Stage IV: Very severe (%)	3.3	15.2	8.4	9.4	1.3	13.5

*Mean (SD) $^{\dagger}p<0.05$; $^{\ddagger}p<0.001$; $^{\S}p<0.0001$ comparing responsive vs. poorly responsive

Table 4: Logistic regression with stepwise selection procedure for each reversibility criterion. Variables were selected from age, gender, smoking status, smoking pack years, COPD duration, baseline % predicted FEV_1 before bronchodilators, and SGRQ total score. Variables with p-value less than 0.05 were kept in the model.

Reversibility criterion	Variables	Odds Ratio	95% CI	p-value
ΔFEV_1 ≥12% and ≥200 ml				
	Female vs. Male	0.610	0.538, 0.691	<.0001
	Age	0.978	0.971, 0.984	<.0001
	Smoking [pk yrs]	1.003	1.001, 1.005	0.0006
	SGRQ	0.985	0.982, 0.989	<.0001
	FEV_1 (% predicted)	0.982	0.978, 0.987	<.0001
ΔFEV_1 ≥15%				
	Female vs. Male	1.371	1.191, 1.578	<.0001
	Smoking [pk yrs]	1.003	1.001, 1.005	0.0135
	SGRQ	0.984	0.981, 0.988	<.0001
	FEV_1 (% predicted)	0.926	0.921, 0.931	<.0001
Δabsolute FEV_1 % predicted ≥10%				
	Female vs. Male	1.314	1.159, 1.490	<.0001
	Smoking [pk ys]	1.003	1.001, 1.005	0.0063
	SGRQ	0.986	0.983, 0.990	<.0001
	FEV_1 (% predicted)	0.988	0.983, 0.992	<.0001

Note: An event in the definition of the odds ratio is a responsive patient according to one of the reversibility criteria. The odd ratios for the continuous variables (age, percent predicted FEV1, SGRQ and smoking pack year) are calculated according to one unit increase of these variables.

LEGEND TO FIGURES

Figure 1: Mean (SD) pre and post bronchodilator spirometry at baseline (N=5,756)

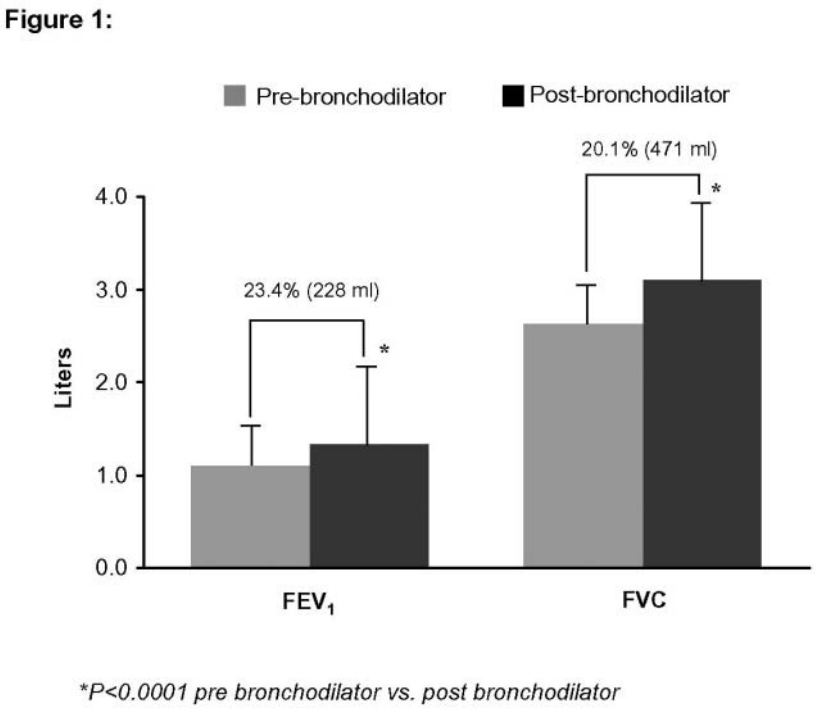


Figure 2: Proportion of patients according to changes in pre to post-bronchodilator FEV_1 (N=5,756). (A) represents percent change in FEV_1. (B) represents absolute change in FEV_1. (C) represents change in FEV_1 percent predicted.

Figure 2A:

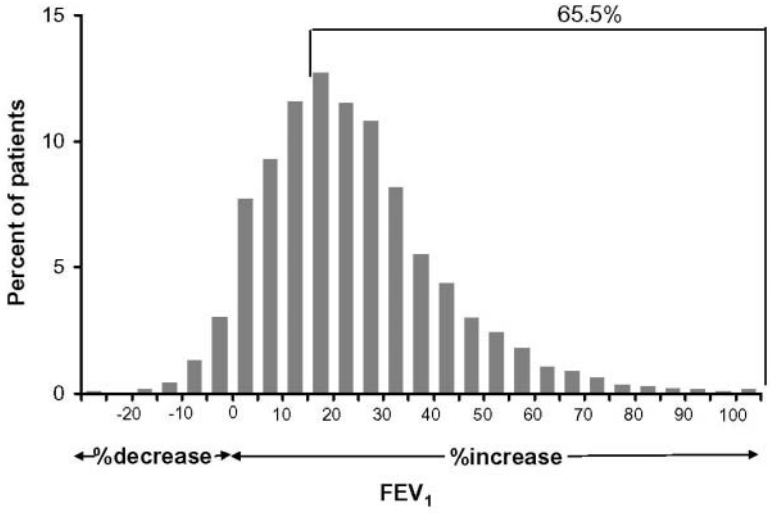

65.5%
15
10
5
0
Percent of patients
-20
-10
0
10
20
30
40
50
60
70
80
90
100
%decrease
%increase
FEV1

Figure 2B:

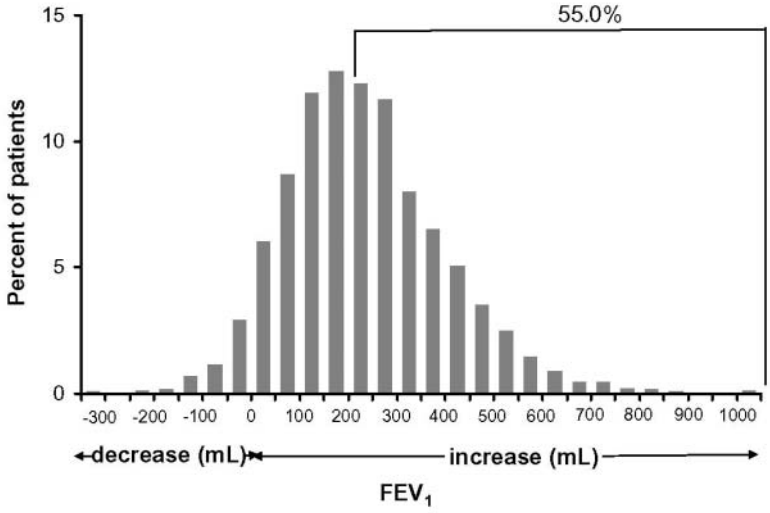

55.0%
15
10
5
0
Percent of patients
-300 -200 -100 0 100 200 300 400 500 600 700 800 900 1000
decrease (mL)
increase (mL)
FEV1

Figure 2C:

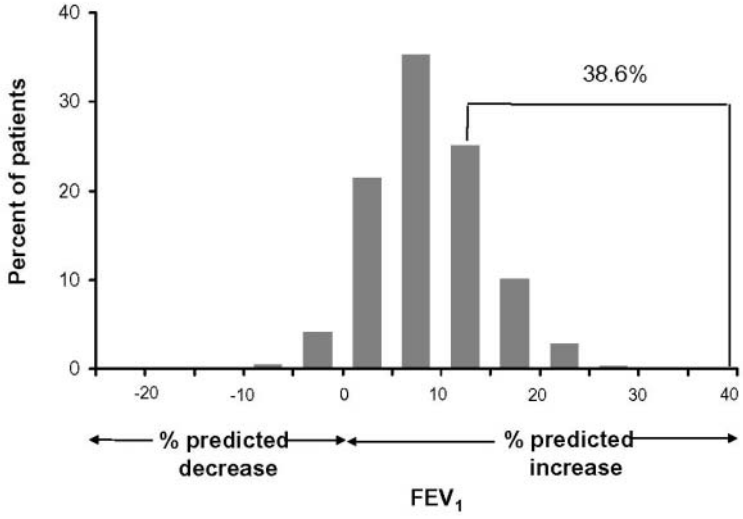
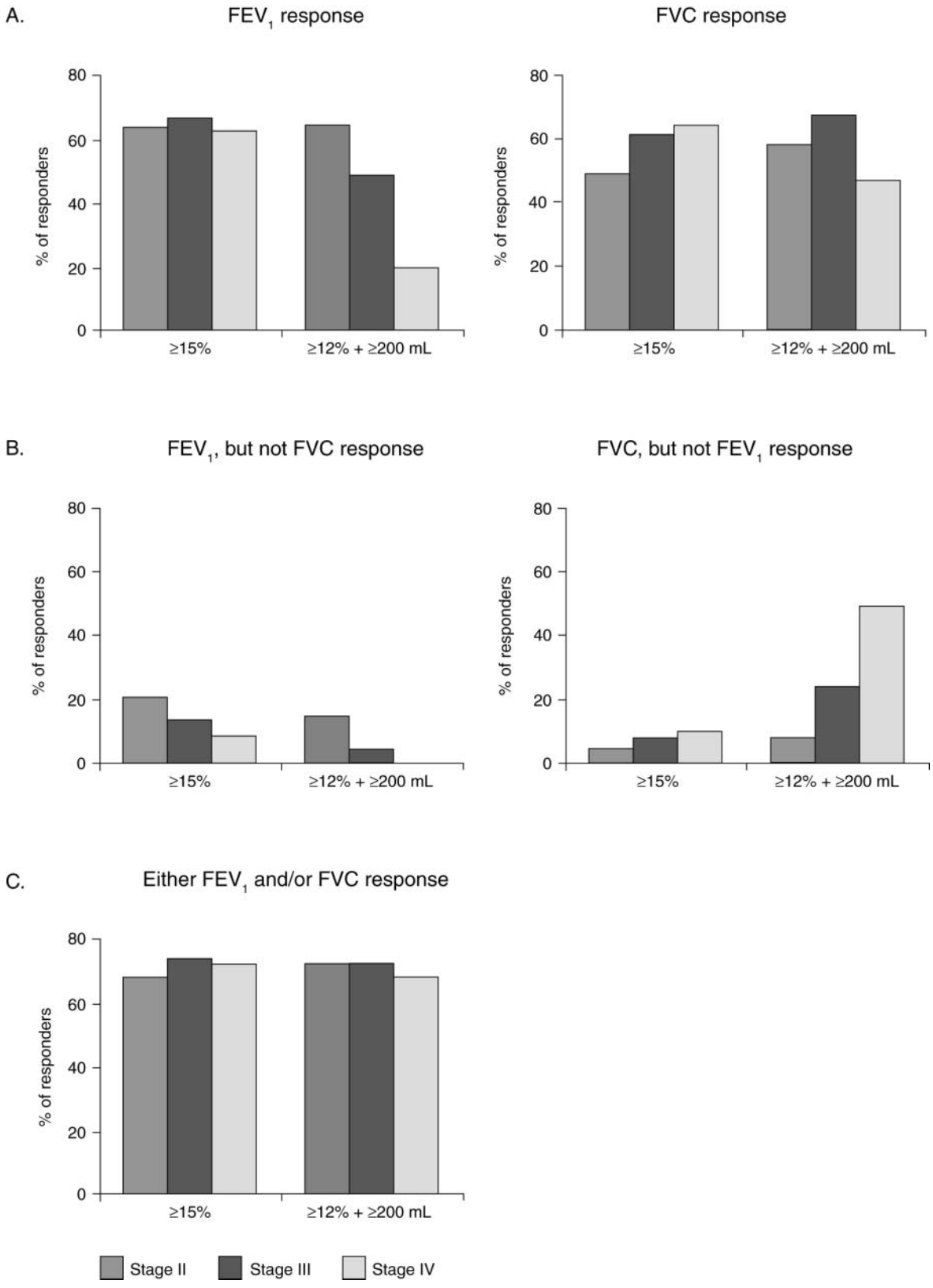


Figure 3: Proportion of patients in GOLD Stages II, III and IV who exhibit bronchodilator responsiveness according to the ≥15% or the ≥12% plus ≥200 ml criteria for FEV_1 and FVC separately (panel A), FEV_1 but not FVC and FVC but not FEV_1 (panel B) and either FEV_1 or FVC (panel C).


A.
FEV1 response
FVC response
% of responders
80
60
40
20
0
≥15%
≥12% + ≥200 mL
B.
FEV1, but not FVC response
FVC, but not FEV1 response
C.
Either FEV1 and/or FVC response
Stage II
Stage III
Stage IV