ORIGINAL ARTICLE

Changes in Forced Expiratory Volume in 1 Second over Time in COPD

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This article (10.1056/NEJMoa1105482) was published on September 26, 2011, at NEJM.org.

N Engl J Med 2011;365:1184-92.

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ABSTRACT

BACKGROUND

A key feature of chronic obstructive pulmonary disease (COPD) is an accelerated rate of decline in forced expiratory volume in 1 second (FEV_1), but data on the variability and determinants of this change in patients who have established disease are scarce.

METHODS

We analyzed the changes in FEV_1 after administration of a bronchodilator over a 3-year period in 2163 patients. A random-coefficient model was used to evaluate possible predictors of both FEV_1 levels and their changes over time.

RESULTS

The mean (±SE) rate of change in FEV_1 was a decline of 33±2 ml per year, with significant variation among the patients studied. The between-patient standard deviation for the rate of decline was 59 ml per year. Over the 3-year study period, 38% of patients had an estimated decline in FEV_1 of more than 40 ml per year, 31% had a decline of 21 to 40 ml per year, 23% had a change in FEV_1 that ranged from a decrease of 20 ml per year to an increase of 20 ml per year, and 8% had an increase of more than 20 ml per year. The mean rate of decline in FEV_1 was 21±4 ml per year greater in current smokers than in current nonsmokers, 13±4 ml per year greater in patients with emphysema than in those without emphysema, and 17±4 ml per year greater in patients with bronchodilator reversibility than in those without reversibility.

CONCLUSIONS

The rate of change in FEV_1 among patients with COPD is highly variable, with increased rates of decline among current smokers, patients with bronchodilator reversibility, and patients with emphysema. (Funded by GlaxoSmithKline; ECLIPSE ClinicalTrials.gov number, NCT00292552.)

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Since the seminal study by Fletcher et al. in the 1970s,[1,2] it has been widely accepted that chronic obstructive pulmonary disease (COPD) is characterized by an accelerated decline in forced expiratory volume in 1 second (FEV$_1$). However, surprisingly few longitudinal studies of patient cohorts have provided detailed data regarding the rate of decline in FEV$_1$,[3-8] and none of these studies have related changes in FEV$_1$ to specific subgroups of patients with COPD or to levels of systemic biomarkers. We used data from a large, observational, 3-year study that included detailed assessments of patients with COPD to examine the variability of changes in FEV$_1$ and to explore whether these changes differed among patient subgroups and whether certain biomarkers could predict changes in FEV$_1$.

METHODS

STUDY DESIGN AND PATIENTS

Our analysis was based on data collected in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) observational study.[9,10] Patients with COPD who were between the ages of 40 and 75 years were enrolled in the study if they had a history of 10 or more pack-years of smoking, as well as an FEV$_1$ that was less than 80% of the predicted value and a ratio of FEV$_1$ to forced vital capacity (FVC) of 0.7 or less; both measurements were made after use of a bronchodilator. Respiratory symptoms, smoking history, occupational exposure, and coexisting medical conditions were documented at study entry with the use of a modified version of the American Thoracic Society–Division of Lung Disease (ATS-DLD) questionnaire.

The study was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent, and the study was approved by the relevant ethics and review boards. The study was conducted in accordance with the protocol, available with the full text of this article at NEJM.org.

STUDY ASSESSMENTS

After the baseline visit, patients returned to their study centers on seven occasions for follow-up assessments: at 3 months and at 6 months and then every 6 months for 3 years. At each visit, the patient reported the number of COPD exacerbations since the last visit. Exacerbations were defined as worsening of COPD symptoms that required treatment with antibiotics or systemic glucocorticoids, alone or in combination, or hospitalization, as reported in more detail previously.[11] At each visit, the severity of COPD was graded according to the stages of disease as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[3]

At baseline and at each subsequent visit, patients underwent spirometry (Viasys MasterScope) before and 15 minutes after inhaling 400 μg of salbutamol from a metered-dose inhaler with the use of a Volumatic spacer (GlaxoSmithKline). Computed tomographic (CT) scanning of the chest was performed at baseline to evaluate the severity and distribution of emphysema. Quantitative assessment of lung volumes and estimation of the percentage of lung CT voxels below a threshold of –950 Hounsfield units was performed with the use of Pulmonary Workstation software, version 2.0 (VIDA Diagnostics).[12]

SUBGROUPS AND BIOMARKERS

Subgroups were based on status with respect to emphysema and chronic bronchitis, bronchodilator reversibility, and cardiovascular disease. Emphysema was defined as more than 10% of lung volume with a density of –950 Hounsfield units or less during a maximal inspiratory breath hold. Chronic bronchitis was defined as the presence of phlegm for periods of 3 months or more for at least 2 years and was assessed on the basis of responses to relevant ATS-DLD questions. Patients were classified as having either emphysema or chronic bronchitis, both entities, or neither entity. Bronchodilator reversibility was defined as an increase in FEV$_1$ that was 12% above the baseline value and at least 200 ml after inhalation of 400 μg of albuterol. Patients were classified as having cardiovascular disease if they reported "heart trouble," hypertension, heart failure, or ischemic heart disease on the ATS-DLD questionnaire.

Serum and plasma samples for biomarker measurements were obtained at baseline and stored at –80°C until they were analyzed. Relationships between changes in FEV$_1$ and circulating levels of C-reactive protein, interleukin-8, interleukin-6, fibrinogen, tumor necrosis factor alpha, surfactant protein D, and Clara cell secretory protein 16 (CC-16) were also measured. Details of the assays are described in the Supplementary Appendix, available at NEJM.org.

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STATISTICAL ANALYSIS

Random-coefficient models with both a random intercept and a random slope were constructed to determine the effect of patient characteristics on post-bronchodilator FEV_1 at baseline and its rate of change over the 3-year study period. Quadratic and piecewise models with fixed and random join points (i.e., the points at which lines with different slopes meet) did not provide substantially better fit than did the linear model. The random slope was based on time of FEV_1 assessment. The final predictors of baseline FEV_1 (i.e., at the time of enrollment) and its rate of change were determined with the use of a series of models that were built up by means of stepwise selection of baseline clinical characteristics, phenotypes of interest, and biomarkers measured at study entry, as well as each covariate's interaction with time. Effect estimates were adjusted for age, sex, height, and weight at study entry; current smoking status and smoking history (pack-years) at study entry; and number of exacerbations during the year before entry. For nonsignificant terms in the models, effect estimates were the model coefficients just before removal from the model. The empirical Bayes estimate of the rate of change in FEV_1 was calculated for each patient and summarized in the form of a histogram (Fig. 1). Comparisons of patient characteristics were carried out by means of analyses of variance, Kruskal–Wallis tests, or chi-square tests, as appropriate; t-tests based on the appropriate linear combinations of the random effects and their standard errors were used to compare the rates of change in FEV_1. P values of less than 0.05 were considered to indicate statistical significance. No adjustments were made for multiple testing. All analyses were conducted with the use of SAS software, version 9.1 (SAS Institute). Additional details about model selection can be found in the Supplementary Appendix.

RESULTS

PATIENT CHARACTERISTICS

A total of 2164 patients were recruited for the study, 1 of whom was subsequently excluded because of inadequate FEV_1 measurements for analyses. Of the remaining 2163 patients, 1447 had eight FEV_1 assessments, 198 had seven, 95 had six, 99 had five, 96 had four, 81 had three, 67 had two, and 80 had only one. The baseline characteristics of the patients are reported in Table 1, categorized according to the number of FEV_1 assessments available for evaluation. Patients with fewer measurements appeared to have more severe disease. Lung function at baseline was associated with age, sex, anthropometric measures, smoking history, and exacerbation history (Table 2). Table 1 in the Supplementary Appendix shows baseline characteristics of the patients according to geographic region.

RATE OF CHANGE IN FEV_1

The mean rate of change in FEV_1 was a decline of 33±2 ml per year, with significant variation in the levels of change (Fig. 1). The between-subjects standard deviation for the decline in FEV_1 was 59 ml per year. Slightly more than one in three participants (38%) had an estimated rate of decline in FEV_1 of more than 40 ml per year over the 3-year period; in 31%, FEV_1 declined by 21 to 40 ml per year, in 23% the change in FEV_1 ranged from a decline of 20 ml per year to an increase of 20 ml per year, and in 8%, FEV_1 increased by more than 20 ml per year. Patients with moderate disease (GOLD stage 2) had a mean rate of decline in FEV_1 of 35±1 ml per year, as compared with declines of 33±1 ml per year in patients with severe disease (GOLD stage 3) and 25±2 ml per year in patients with very severe disease (GOLD stage 4) ($P=0.17$ for stage 2 vs. stage 3, $P<0.001$ for stage 2 vs. stage 4, $P=0.009$ for stage 3 vs. stage 4).

The rate of change was not associated with the number of FEV_1 measurements. The mean rate of decline for patients with seven or eight assessments was 32±1 ml per year, as compared with 37±2 ml per year for those contributing four, five, or six measurements and 31±3 ml per year for those with one, two, or three measurements. Although 10% of the patients died and 13% withdrew from the study, the mean rates of change did not differ significantly among those who died, those who withdrew, and those who completed the study (Table 2 in the Supplementary Appendix). We did not see an increasing rate of decline with an increase in age or cumulative tobacco exposure, expressed as pack-years of smoking. Although men had higher levels of post-bronchodilator FEV_1 at baseline, the rate of change was similar for men and women. The rate of decline in FEV_1 was affected by smoking status, with a decline of 21±4 ml per year more among current smokers than among former smokers. FEV_1 at baseline was lower in patients who reported more exacerbations in the year before study entry, but

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the number of prior exacerbations had no effect on the subsequent rate of change. Exacerbations during follow-up, however, were associated with an excess decline in FEV_1, with a mean loss of 2±0.5 ml per year per exacerbation (Table 2).

ANALYSIS OF SUBGROUPS

Patients with chronic bronchitis did not have a more rapid rate of decline in FEV_1 but did have a lower mean FEV_1 (43±20 ml per year) at baseline than did patients without chronic bronchitis. Patients with bronchodilator reversibility at baseline had a mean FEV_1 that was 220±22 ml per year higher than did patients without reversibility at baseline, and their FEV_1 declined by an additional 17±4 ml per year. The presence or absence of self-reported cardiovascular disease affected neither FEV_1 at baseline nor its rate of change. In the subset of patients for whom CT data were available (1807 patients), the mean FEV_1 at baseline was 327±21 ml lower in those with clinically significant emphysema (>10% low-attenuation areas) than in those with little or no emphysema, and FEV_1 declined by an additional 13±4 ml per year.

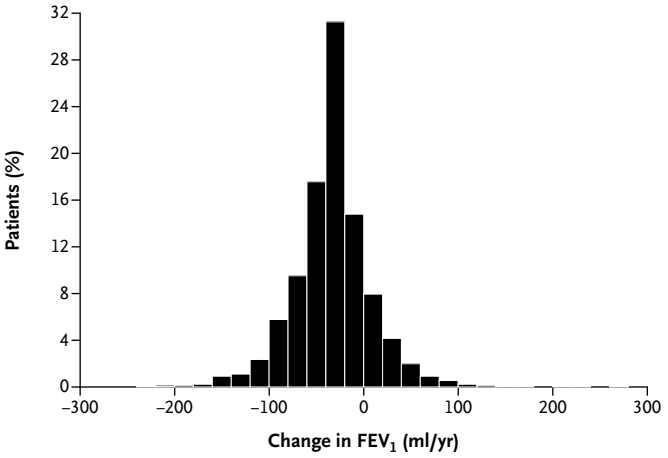

Figure 1. Distribution of Estimated Annual Rates of Change in Forced Expiratory Volume in 1 Second (FEV_1) over a 3-Year Period in Patients with Chronic Obstructive Pulmonary Disease.

Empirical Bayes estimates of the change in FEV_1 were calculated for each patient with the use of the random-coefficient model and are summarized in the form of a histogram. Each bar represents a change in FEV_1 of 20 ml per year.

ANALYSIS OF BIOMARKERS

We analyzed data for the subset of patients for whom data on all biomarker values were available (1793 patients); the results of these analyses were not corrected for multiple testing. Several of the biomarkers we examined were associated with FEV_1 at baseline (Table 3). This association was most pronounced for fibrinogen, for which the difference in FEV_1 associated with an increase of 1 SD was similar to the difference in FEV_1 between current and former smokers. Only CC-16 levels were significantly associated with the rate of change in FEV_1, with an additional decline of 4±2 ml per year for each decrease of 1 SD in the level of CC-16. The association between the CC-16 level and the rate of decline in FEV_1 was not modified by age, sex, GOLD stage, current smoking status or smoking history, or patient subgroup. Neither surfactant protein D nor any of the biomarkers believed to reflect systemic inflammation were related to a change in FEV_1 over time (Table 3).

DISCUSSION

In this observational study of patients with COPD, we found that the rate of decline in FEV_1 over a 3-year period was highly variable. Although COPD is considered to be a progressive disease, only 38% of patients had an estimated rate of decline in FEV_1 of more than 40 ml per year. Current smoking was most strongly associated with the rate of decline in FEV_1. In addition, patients with emphysema (as defined on the basis of CT scanning) and patients with bronchodilator reversibility both had an excess loss of FEV_1 over the 3-year study period, as compared with the study participants who did not have these conditions. None of the biomarkers were strongly associated with a decline in FEV_1; however, the baseline level of CC-16 was associated with the rate of decline and may possibly serve as a biomarker of disease progression, if this finding can be replicated in other populations.

The relatively modest declines in lung function observed in the current study are not substantially different from those reported in the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial (ClinicalTrials.gov number, NCT00144339), in which the mean rate of decline in FEV_1 over a period of 4 years was 41 ml per year.[8] In addition, when assessed according to the severity of airflow limitation, the rate of decline appears to be inversely related to the GOLD stage; this observation is consistent with the findings in both the UPLIFT study and the To-

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wards a Revolution in COPD Health (TORCH) study (ClinicalTrials.gov number, NCT00268216).[7]

Our study had several limitations. First, it included only patients with moderate, severe, or very severe COPD and thus cannot identify factors of importance that are associated with rates of decline in early-stage COPD. Epidemiologic studies have identified the presence of breathlessness[13] and bronchial hyperreactivity[14] as indicators of progressive loss of lung function, but recruitment for these studies and for ECLIPSE differed so much that a direct comparison is impossible.

Second, all the patients in our study received treatment for their COPD, which was managed by their usual physicians. Although none of the drugs available for the treatment of COPD have been shown unequivocally to reduce the decline in FEV_1,[3] a secondary analysis in the TORCH study indicated that declines in FEV_1 may be reduced with regular treatment,[15] and similar indications were evident in subgroup analyses in the UPLIFT trial.[16] Our study was purely observational, and we chose not to include treatment in our analyses, since the effects of treatment on the rate of decline in FEV_1 are likely to be confounded as a result of bias by indication and other biases that are characteristic of observational pharmacoepidemiologic studies. Moreover, the diagnosis and management of COPD in the patients in our study were carried out at specialist centers, and our results may not extend beyond this patient population for a variety of reasons, including the clinically determined care they received. An estimated 15% of the patients assessed in our study had

Table 1. Characteristics of the Patients According to Number of Measurements of Forced Expiratory Volume in 1 Second (FEV_1).*

Characteristic	All Patients (N=2163)	No. of Assessments			P Value†
		7 or 8 (N=1645)	4 to 6 (N=290)	1 to 3 (N=228)	
Age (yr)	63±7	63±7	65±7	64±8	0.001
Female sex (%)	35	35	33	34	0.80
Smoking status					
Current smoker (%)	36	34	40	44	0.006
Smoking history (pack-yr)	49±27	48±27	53±29	51±27	0.004
Body-mass index‡	27±6	27±6	26±6	26±6	0.46
FEV_1 after bronchodilator use					
Value (liters)	1.35±0.52	1.39±0.52	1.20±0.52	1.21±0.50	<0.001
Percent of predicted value	48±16	50±16	44±16	44±15	<0.001
Exacerbations (no.)					
In yr before study	0.8±1.2	0.8±1.1	1.0±1.4	0.9±1.3	0.001
First yr of study	1.2±1.5	1.1±1.4	1.7±2.0	0.9±1.4	<0.001
Phenotype (%)					
Emphysema	67	66	70	71	0.24
Chronic bronchitis	35	34	38	39	0.12
Emphysema and chronic bronchitis	22	21	23	24	0.56
Neither emphysema nor chronic bronchitis	23	24	17	16	0.002
COPD and CVD	56	54	60	59	0.09
Treatment (%)					
Inhaled glucocorticoids	72	71	73	73	0.66
Long-acting beta-agonists	68	68	70	67	0.62
Tiotropium	46	46	49	42	0.22

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Table 1. (Continued.)

Characteristic	All Patients (N=2163)	No. of Assessments			P Value†
		7 or 8 (N=1645)	4 to 6 (N=290)	1 to 3 (N=228)	
Biomarkers					
C-reactive protein (μg/ml)					0.07
Mean	3.2	3.1	3.2	4.3	
Interquartile range	1.5–7.3	1.6–6.8	1.5–7.9	1.3–11.7	
Interleukin-6 (pg/ml)					<0.001
Mean	1.5	1.4	1.9	2.5	
Interquartile range	0.8–3.1	0.7–2.7	0.9–3.9	1.1–4.8	
Interleukin-8 (pg/ml)					0.015
Mean	7.1	6.9	7.8	7.8	
Interquartile range	3.4–13.2	3.3–12.4	3.6–17.3	3.5–15.2	
Fibrinogen (mg/dl)					0.007
Mean	449	444	465	456	
Interquartile range	389–518	388–512	394–535	391–541	
TNF-α (pg/ml)					0.40
Mean	2.4	2.4	2.4	2.4	
Interquartile range	2.4–11.7	2.4–15.2	2.4–7.2	2.4–2.4	
CC-16 (ng/ml)					0.26
Mean	5.0	5.0	5.3	4.7	
Interquartile range	3.5–7.0	3.4–6.9	3.7–7.5	3.5–7.0	
Surfactant protein D (ng/ml)					<0.001
Mean	120	117	124	139	
Interquartile range	84–172	84–165	83–188	93–206	

* Plus–minus values are means ±SD. CC-16 denotes Clara cell protein 16, COPD chronic obstructive pulmonary disease, CVD cardiovascular disease, and TNF-α tumor necrosis factor alpha.
† P values are for the overall comparison of the three subject groups (determined by the number of assessments) and are based on analyses of variance, Kruskal–Wallis tests, and Cochran–Mantel–Haenszel tests, as appropriate.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

improved lung function over the 3-year study period. Whether this represents an expected statistical distribution or a true response to treatment is unknown. However, the possibility that some patients with COPD might have improvement over time was noted by Fletcher et al.[2]

Patients who continued to smoke were at increased risk for marked progression, as compared with former smokers, and this remained true irrespective of the GOLD stage. In contrast, cumulative exposure did not affect future decline. This finding points to smoking cessation as the most important tool in secondary and tertiary prevention for patients at all stages of COPD.[1] Exacerbations had an effect on the rate of decline in FEV$_1$, but this effect was very modest, as compared with the effect of smoking. The effect of exacerbations was also similar to that found in the Lung Health Study[17] but was smaller than the effects in other studies[18,19]; however, because studies differ considerably in design and inclusion criteria, direct comparisons are difficult. In our study, the association between bronchodilator reversibility and the rate of decline in FEV$_1$ is more difficult to interpret. Reversibility is known to be an unstable phenomenon[20] that does not predict mortality when post-

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Table 2. Effects of Patient Characteristics on Baseline Forced Expiratory Volume in 1 Second (FEV_1) and on Annual Rate of Change in FEV_1.*

Characteristic	Effect on Baseline FEV_1	P Value	Effect on Annual Rate of Change in FEV_1	P Value
	ml		*ml/yr*	
Age (per yr)	−10±1.4	<0.001	0±0.3	0.21
Female sex	−55±26.0	0.04	3±3.8	0.42
Height (per cm)	19±1.5	<0.001		
Weight (per kg)	5±0.6	<0.001		
Smoking status				
Current smoker (yes vs. no)	102±20.7	<0.001	−21±3.8	<0.001
Smoking history (per pack-yr)	−1±0.4	0.02	0±0.1	0.20
Prior exacerbations				
≥3 vs. 0	−259±34.3	<0.001	−3±6.7	0.67
≥3 vs. 1	−107±37.1	0.004	2±7.2	0.83
≥3 vs. 2	−47±41.6	0.25	−5±8.1	0.57
Exacerbations during follow-up (per exacerbation)			−2±0.5	<0.001
Bronchodilator reversibility (yes vs. no)	220±22.4	<0.001	−17±4.2	<0.001
Emphysema (yes vs. no)	−327±21.2	<0.001	−13±4.2	0.002
Chronic bronchitis (yes vs. no)	−43±20.2	0.033	−2±3.8	0.67
Cardiovascular disease (yes vs. no)	11±19.7	0.57	1±3.6	0.77

* Plus–minus values are means ±SE.

Table 3. Effects of Biomarkers on Forced Expiratory Volume in 1 Second (FEV_1).*

Biomarker†	Effect on Baseline FEV_1	P Value‡	Effect on Annual Rate of Change in FEV_1	P Value‡
	ml		*ml/yr*	
Fibrinogen	−93±10.6	<0.001	−1±2.1	0.63
Interleukin-6	0±10.0	>0.99	1±2.3	0.52
Interleukin-8	20±9.9	0.04	−2±2.0	0.36
TNF-α	1±9.9	0.89	0±1.8	0.84
C-reactive protein	−23±10.3	0.037	4±2.1	0.07
CC-16	33±10.8	0.002	4±2.2	0.04
Surfactant protein D	0±10.3	0.96	−3±2.1	0.18

* Plus–minus values are means ±SE.
† Effects are per increase of 1 SD in the values of the individual biomarkers (i.e., a change of 1 SD in the level of the biomarker resulted in a specific effect on FEV_1). CC-16 denotes Clara cell protein 16, and TNF-α tumor necrosis factor alpha.
‡ P values were not corrected for multiple testing.

bronchodilator FEV_1 is taken into account.[21] Furthermore, analyses of the larger Lung Health Study, which involved patients who had milder disease than the patients in our study, and the smaller Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study, which involved patients with more severe disease, did not show an association between reversibility and rate of decline.[20,22] Our definition of reversibility, which included both a relative and an absolute criterion, may have led to the association we observed — a possibility that should be examined in replication studies.

We studied a number of biomarkers and found that only one, CC-16, was associated with the rate

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of decline in FEV_1. This association was weak, and whether it is biologically meaningful has yet to be determined. Without confirmation, it does not seem appropriate to speculate on the potential significance of this finding. The list of potentially valuable biomarkers is long[23] and growing. Other markers will undoubtedly be tested in other studies.

In conclusion, our data show that COPD is not invariably progressive. In more than half the patients in our study, the rate of decline in FEV_1 over a period of 3 years was no greater than that which has been observed in people without lung disease. This finding could indicate that COPD may "burn out" or at least stabilize for periods of 3 years or more, which would be good news for patients and could influence a variety of management decisions that depend on prognosis. The continuation of smoking is strongly associated with an increased rate of decline in FEV_1, a finding that underscores the importance of smoking cessation for patients with this condition. Since our findings challenge the concept that progressive loss of lung function is inevitable in COPD, they should spark interest in revising our view of the course of this condition.

Supported by grants from GlaxoSmithKline (to Drs. Vestbo, Scanlon, Agusti, Bakke, Calverley, Celli, Coxson, Lomas, MacNee, Silverman, Wouters, and Rennard).

Dr. Vestbo reports receiving consulting fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Nycomed, and Pfizer, speaking fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Nycomed, and grants on behalf of his institution from GlaxoSmithKline; Dr. Scanlon, receiving travel support from Boehringer Ingelheim and Novartis and receiving grants from Boehringer Ingelheim, Forest Laboratories, GlaxoSmithKline, Pfizer, and Novartis on behalf of his institution; Dr. Agusti, receiving fees for serving on the boards of Almirall, AstraZeneca, Boehringer Ingelheim, Esteve, GlaxoSmithKline, Novartis, Nycomed, and Roche, speaking fees from Almirall, AstraZeneca, Boehringer Ingelheim, Esteve, GlaxoSmithKline, and Nycomed, payment for the development of educational presentations from Nycomed, and receiving grants from Almirall, GlaxoSmithKline, and Nycomed on behalf of his institution; Dr. Bakke, receiving speaking fees from AstraZeneca, GlaxoSmithKline, and Pfizer; Dr. Calverley, receiving fees for serving on the boards of GlaxoSmithKline, Boehringer Ingelheim, and Nycomed, consulting fees from Merck and Novartis, payment for providing expert testimony for Forest, speaking fees from AstraZeneca and GlaxoSmithKline, travel support from Boehringer Ingelheim, and receiving speaking fees from Novartis and Pfizer on behalf of his institution; Dr. Celli, receiving consulting fees from Aeris, Almirall, AstraZeneca, Boehringer Ingelheim, Novartis, and Rox Medical; Dr. Coxson, receiving consulting fees from GlaxoSmithKline and Spiration, speaking fees from AstraZeneca, travel support from AstraZeneca and Spiration, and receiving grants from GlaxoSmithKline and Spiration on behalf of his institution; Dr. Lomas, receiving fees for serving on the board of GlaxoSmithKline, consulting fees from GlaxoSmithKline, speaking fees from GlaxoSmithKline, travel support from Boehringer Ingelheim and GlaxoSmithKline, and receiving grants from GlaxoSmithKline on behalf of his institution; Dr. MacNee, receiving travel support from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Pfizer, and he and his institution receiving consulting fees from Pfizer and fees for membership on the boards of Pfizer and GlaxoSmithKline; Dr. Rennard, receiving fees for membership on the boards of Almirall, Novartis, Nycomed, and Pfizer, consulting fees from Able Associates, Adelphi Research, APT Pharma/Britnall, Aradigm, AstraZeneca, Boehringer Ingelheim, Chiesi, CommonHealth, Consult Complete, COPDforum, Datamonitor, Decision Resources, Defined Health, Dey, Dunn Group, Easton Associates, Equinox, Forest, Gerson, GlaxoSmithKline, InfoMed, KOL Connection, M. Pankove, MedaCorp, MDRx Financial, Mpex, Novartis, Nycomed, Oriel Therapeutics, Otsuka, Pennside, Parma Ventures, Pearl, Pharmaxis, Price Waterhouse, Propagate, Pulmatrix, Reckner Associates, Recruiting Resources, Roche, Sankyo, Schlesinger Medical, Scimed, Sudler and Hennessey, TargeGen, Theravance, United BioSource, Uptake Medical, and VantagePoint Management, speaking fees from AstraZeneca, Convergent Health Solutions for Reviews and Trends in COPD, COPD Foundation, Creative Educational Concepts, Dey, France Foundation, Information TV, Network for Continuing Education (CHARM), Novartis (Horsham), Nycomed, Otsuka, and Pfizer, travel support from Almirall, AstraZeneca, Boehringer Ingelheim, California Allergy Society, Creative Educational Concept, France Foundation, GlaxoSmithKline, Information TV, Network for Continuing Education, Novartis, Nycomed, and Pfizer, and receiving grants from AstraZeneca, Biomarck, Boehringer Ingelheim, Centocor, Mpex, Nabi, Novartis, Nycomed, and Otsuka on behalf of his institution; Dr. Silverman, receiving consulting fees from AstraZeneca and GlaxoSmithKline, speaking fees from AstraZeneca and GlaxoSmithKline, and receiving grants from GlaxoSmithKline on behalf of his institution; and Dr. Wouters, receiving fees for membership on the board of Nycomed, speaking fees from AstraZeneca, GlaxoSmithKline, and Novartis, and grants from AstraZeneca and GlaxoSmithKline. Drs. Crim, Edwards, Miller, Tal-Singer, and Yates report being employees of and owning stock in GlaxoSmithKline. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank all the study participants for their willingness to advance medical science in the field of COPD, Drs. Nestor Müller and Paola Nasute Fauerbach for their radiologic expertise in the assessment of emphysema, and Tara Candido, Sebastian Cogswell, Heather Davis, Nima Farzaneh, Lukas Holy, Natasha Krowchuk, Helena Lee, Evan Phillips, Claudine Storness-Bliss, Nerissa Tai, Anh-Toan Tran, Nghia Tran, Eugene Wang, and Tomonori Yokogawa for technical assistance with the CT analysis and data management.

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