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Implications of the GOLD 2011 Disease Severity Classification in the COPDGene Cohort

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Abstract

Background—The 2011 Global Strategy for the Diagnosis, Management, and Prevention of COPD (GOLD) consensus report uses symptoms, exacerbation history and FEV₁% to define four categories: A, low symptoms/low risk; B, high symptoms/low risk; C, low symptoms/high risk; and D, high symptoms/high risk where risk refers to exacerbations, hospitalization and death. Our

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Contribution of co-authors

MKH, MD, GW, RB, DL, AA, FM, JC, ES and BM aided with data collection. MH and DC performed data analysis. MKH, HM, DCE, MD, GW, ER, RB, TB, JH, DL, PJ, AA, FM, JC, ES and BM all contributed to data interpretation and manuscript preparation.

objective was to determine (1) the influence of symptom instrument on category membership and (2) prospective exacerbation risk by category.

Methods—4,484 COPD subjects from COPDGene were analyzed. All subjects had smoking history ≥ 10 pack-years and $FEV_1/FVC < 0.7$. Categories were defined using the modified Medical Research Council Dyspnea [mMRC] (0–1 versus ≥ 2) and the Saint George's Respiratory Questionnaire [SGRQ] (≥ 25 versus < 25 as a surrogate for the COPD Assessment Test ≥ 10 versus < 10) in addition to COPD exacerbations in the prior year (≥ 2 versus < 2), and $FEV_1\%$ predicted (≥ 50 versus < 50).

Findings—Category assignment using mMRC versus SGRQ were similar but not identical. Using the mMRC, category assignments were 34% A, 21% B, 8% C and 38% D and for SGRQ were 29% A, 25% B, 5% C and 41% D ($\kappa = 0.77$). Significant heterogeneity in exacerbation rates (exacerbations/person-year) were seen particularly within the D group, depending on the risk factor that determined category assignment (lung function (0.89), prior exacerbation history (1.34) or both (1.86), $p < 0.001$).

Interpretations—The GOLD classification emphasizes the importance of symptoms and exacerbation risk in assessing COPD severity. The choice of symptom measure influences category assignment. The relative number of subjects with low symptoms and high risk for exacerbations (category C) is low. Differences in exacerbation rates for subjects in the highest risk category D were seen depending on whether risk was based on lung function, exacerbation history or both.

INTRODUCTION

The development of a disease staging system in COPD to assess severity and determine treatment algorithms has proven challenging. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2006 staging system used forced expiratory volume (FEV_1) to determine disease severity.¹ In large population studies, lung function correlates reasonably well with many disease outcomes but is poorly predictive of dyspnea, quality of life and exacerbation frequency.^{2,3} Lung function alone does not completely capture the heterogeneity present within the COPD patient population.⁴ Hence, the GOLD 2011 consensus report proposed a new classification system for COPD (Figure 1) to more comprehensively assess disease severity,⁵ incorporating symptoms using either a dyspnea measure (the modified Medical Research Council [mMRC] dyspnea score) or a health status measure (the COPD Assessment Test [CAT] score) in addition to COPD exacerbation history and airflow limitation measured by FEV_1 . Our objectives were to use the COPDGene cohort to determine whether (1) the choice of a symptom versus health status measure significantly influences baseline category assignment and (2) whether the categories differ, particularly with respect to exacerbation risk.

METHODS

Overview

The COPDGene® Study (<http://www.copdgene.org>) is an NHLBI-funded multicenter investigation of the genetic epidemiology of smoking-related lung disease. Recruitment

occurred at 21 academic clinical centers (see acknowledgements). However, participants were recruited through a wide variety of mechanisms including general public advertising and screening of primary care and pulmonary clinics. Subjects were eligible if they were aged 45–80 years and had smoked ≥ 10 pack years. A full list of inclusion and exclusion criteria has been described previously.⁶ Subjects were enrolled from January 2008 through April 2011. Subjects included in this analysis were from the April 2012 10,300 dataset, and included all subjects with a post-bronchodilator FEV₁/FVC ratio ≥ 0.7 . All participants provided written informed consent. The research protocol was approved by the participating centers' ethics and review boards.

Data Collection and Exacerbation Determination

Self-administered questionnaires captured demographic data and medical history. Symptoms were quantified with both the mMRC⁷ and the SGRQ.⁸ As the GOLD 2011 report indicates that either symptom measure can be used, we determined the distribution of subjects in GOLD categories independently using first the mMRC (dyspnea) and then the SGRQ (health status). The GOLD 2011 classification (Figure 1) stratifies first based on symptoms using either dyspnea (mMRC 0–1 versus ≥ 2) or health status (CAT <10 or ≥ 10) score resulting in two low symptom categories (A & C) and two high symptom categories (B & D). While the CAT instrument was not used in the COPDGene study, it has been previously shown that a CAT score of 10 (0–40 scaling range) is comparable to an SGRQ score of 25 (0–100 scaling range); available data shows that 31% of CAT scores will differ from the equivalent SGRQ score by a difference of $\leq 5\%$, 60% will differ by a difference of $\leq 10\%$ and 90% will differ by a difference of $\leq 20\%$.^{9, 10} Hence an SGRQ score of 25 was used as a substitute measure for the CAT. Further outlined in the GOLD 2011 report, exacerbation risk is determined using either airflow limitation measured by FEV₁% predicted ($<$ or $\geq 50\%$) or COPD exacerbation history (0–1 versus ≥ 2) in the prior year to stratify patients into low risk (A & B) versus high risk (C & D) categories (see Figure 1). Additionally, the GOLD 2011 report outlines that where exacerbation risk as determined by FEV₁ or prior exacerbation history is not identical, risk should be determined by the method indicating the higher risk.⁵ For this analysis we have further stratified these subjects. In addition to meeting symptom criteria for their respective categories, patients in C1 and D1 categories meet FEV₁ criteria only for C and D, respectively; C2 and D2 meet exacerbation criteria only; C3 and D3 meet both exacerbation and FEV₁ criteria.

Exacerbations were defined by use of an antibiotic and/or steroid or admission to the hospital for a respiratory “flare-up” on the ATS Respiratory Disease questionnaire.¹¹ Severe exacerbations were defined as those requiring assessment in the Emergency Department or hospital admission. Exacerbation history in the prior year was collected at baseline. Prospective exacerbation data was captured through a longitudinal follow-up protocol conducted every six months by an automated telephonic or web based inquiry. Subjects not reached by the automated system were contacted by a research coordinator. Prospective exacerbation rates were calculated in all COPD subjects where longitudinal follow-up data was available (N=3,723). Length of follow-up varied based on time of enrollment (January 2008 through April 2011) with a mean follow-up period of 20 months. April 2012 was used as the cutoff date for available longitudinal data.

Physiologic testing

Patients underwent standardized spirometry before and after the administration of 180 mcg of inhaled albuterol. Independent review of spirometric tracings were conducted to ensure quality control of spirometry data.¹² All subjects underwent standard six minute walk distance (6MWD). BODE index was calculated using as previously described.¹³

Statistical Analyses

All data are presented as means with standard deviations where appropriate. These analyses were performed using SAS 9.2 (Cary, NC). Statistical comparisons were performed using k-sample permutation tests using R (R: A Language and Environment for Statistical Computing; www.R-project.org). 95% confidence intervals were estimated by traditional normal-theory method and verified by 10,000 bootstrap replications.

Role of the funding sources

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RESULTS

Table 1 shows the distribution of subjects into GOLD 2011 categories. Supplemental Table 1 provides the distribution of subjects based on the GOLD 2006 staging system¹ using FEV₁ alone. Of the 4,484 GOLD I–IV COPDGene subjects, using the mMRC, the distribution of A–D was 33.6%, 20.5%, 7.9%, and 38.0% respectively. Using the SGRQ, the distribution is roughly but not exactly similar, 29.4%, 24.8%, 4.9%, and 41.0% classified as A–D respectively. The Kappa coefficient of agreement for subject classification by the two symptom measures was 0.77, indicating good but not identical agreement. Figure 2 provides the distribution of SGRQ scores across mMRC dyspnea grades. From Figure 2, it is evident that some subjects may report no (0) or mild (1) dyspnea but also still report very poor health status (high SGRQ scores). Supplemental Tables 2a and b demonstrate reassignment of subjects and classification agreement based on symptom measure choice. The largest area of disagreement appears to be group C, where 46.7% of patients categorized as “C” via the mMRC would have been classified identically by the SGRQ; 75.1% of subjects categorized as “C” via the SGRQ would have been classified identically by the mMRC. It is also apparent that relatively few subjects are classified as C, regardless of the symptom measure chosen. Additionally, the majority of the C and D membership are comprised by subjects that met FEV₁ criteria alone (C1 and D1) as opposed to exacerbation criteria (C2 and D2) or the combination of exacerbation and FEV₁ criteria (C3 and D3).

Analyses from this point forward will focus on the SGRQ score as the available evidence suggests that the both the SGRQ and CAT are both more repeatable and more sensitive to change than the mMRC.^{14–18} Table 3 further describes characteristics of subjects by GOLD categories. Means, standard deviations and 95% confidence intervals are displayed where appropriate. As compared to GOLD B subjects, GOLD A subjects had better lung function (mean FEV₁% 78 versus 68, $p < 0.001$), lower symptom scores (mean SGRQ 11 versus 45,

$p<0.001$), and in longitudinal follow-up had lower exacerbation rates (0.17 versus 0.55, $p<0.001$).

While SGRQ scores are similar within the C and D subcategories, significant variability exists within these subcategories otherwise. While exacerbation rates were not statistically different for C subcategories, D subcategory subjects did have significantly different exacerbation rates ($p<0.001$). Exacerbation rates were highest for D3 (met exacerbation and FEV₁ criteria) at 1.86 exacerbations/person-year, followed by D2 (met exacerbation criteria) at 1.34 exacerbations/person-year and D1 (met FEV₁ criteria) at 0.89 exacerbations/person year. Severe exacerbation rates followed a similar trend, with rates of 0.62, 0.57, and 0.27 in the D3, D2 and D1 categories respectively ($p<0.001$). Lung function also differs significantly within this group with the FEV₁ 41%, 65% and 32% of predicted ($p<0.001$) for D3-D1 respectively. It is also interesting to note that at least in terms of exacerbation frequency, there appears to be no significant difference in prospectively evaluated total exacerbation rates between B (0.55 exacerbations / person-year) or any of the C subgroups (C1 0.58, C2 0.52, C3 1.39, $p=0.35$) or severe exacerbation rates between B (0.13) and any of the C subgroups (C1 0.06, C2 0.13, C3 0.11, $p=0.23$). However, the low number of subjects in the C groups and relatively wide confidence intervals limit our power to compare the C subgroups.

Medication use based on the GOLD 2011 consensus report recommended therapeutic regimens are outlined in Supplemental Table 3. The percentage of subjects on any recommended medication regimen increases with GOLD category severity. Use of LAMA alone exceeded use of LABA alone for A and B subjects with 6.6% of A and 27.1% of B subjects on LAMA alone versus 1.1% of A and 6.6% of B subjects on LABA alone. The use of a long acting muscarinic antagonist (LAMA) / long acting beta agonist (LABA) regimen as recommended for C and D subjects was generally low, 2.7% of C and 7.8% of D subjects respectively. ICS/LABA was the most common combination therapy. The use of inhaled corticosteroid (ICS) / LAMA regimen as recommended for C and D was also low with 0% and 9.3% of subjects respectively. Use of triple combination therapy with ICS/LABA/LAMA was 0% of C subjects and 43.7% of D subjects.

DISCUSSION

The GOLD 2011 consensus report outlines a new classification system for COPD combining spirometry, symptom assessment and exacerbation risk to identify disease severity and appropriate therapeutic regimens. This approach follows available evidence demonstrating that current therapies can improve lung function and reduce symptoms and exacerbation frequency.^{19, 20} It is important that data be generated to assess the validity of this method. We hypothesized that analysis of the COPDGene cohort would provide insight into the practical application of this approach. In this work we reveal that a) choice of symptom measure, dyspnea (mMRC) versus health status (SGRQ as a surrogate for the CAT) can alter category assignment; b) the relative number of subjects with low symptoms and high risk, category C, is very small; c) the apparent risk for exacerbations in category C also does not appear to be substantially different from category B (high symptoms with low risk for exacerbations), although the relatively small number of subjects may limit our

power to detect differences; and d) for category D subjects with the greatest symptoms and risk for exacerbations, the reason for category assignment (lung function and exacerbation history versus lung function alone versus exacerbation history alone) significantly alters future exacerbation risk.

In comparing the mMRC to SGRQ, a very wide range of SGRQ scores was seen at every mMRC level. The SGRQ and CAT are multidimensional instruments and assess not only dyspnea but also cough, sputum production, fatigue and the impact of these symptoms on activities and daily life¹⁴ such that imperfect correlation between them and the mMRC is not surprising. As the category assignments produced by each symptom measure are not identical, it would seem that a potential refinement of the GOLD classification schema would be to choose one measure only. In practice, an advantage to the mMRC is its brevity, but it only addresses disability due to breathlessness. However, the CAT which was also proposed by GOLD and strongly correlates with SGRQ has broader coverage of the impact of the disease. The CAT has documented good repeatability⁹ and is responsive both to pulmonary rehabilitation^{21, 22} as well as exacerbation onset and recovery^{22, 23} suggesting the CAT may make a better choice than the mMRC.

Another interesting finding was that category C was relatively small, suggesting it is unusual for subjects who are at high risk for exacerbations to also not report significant symptoms. In point of fact, even for the few category C subjects we do report, the exacerbation frequency of this “low symptom / high risk” group is no different from the category B “high symptom / low risk” group. These data would suggest that from a therapeutic standpoint, it is symptoms that differentiate the B and C categories. In general it is the D group that experiences the most exacerbations and severe exacerbations. However, among D subjects, significant heterogeneity exists between D1, D2 and D3 based on reason for assignment to that category: exacerbation history and FEV₁%, exacerbation history alone or airflow limitation alone. The small number of C subjects limits our power to compare differences between C1, C2, and C3 categories. Total exacerbation frequency and severe exacerbation frequency are highest for D3 subjects who meet both exacerbation history and lung function risk factors versus either alone. In practice, more D3 subjects are on ICS / LABA and LAMA therapies than D1 or D2 subjects suggesting that 1) higher exacerbation rates for D3 are not related to less intense therapy and 2) clinicians are already more aggressive in treating this category. Of additional note, the D1 subcategory defined by FEV₁% is by far the largest subcategory suggesting that treatment recommendations for the D category should aim to target these subjects. D2 subjects, while less frequent than D1, notably have much higher lung function suggesting mechanism for exacerbations may differ in this subcategory.

We acknowledge limitations to our analysis. The COPDGene cohort is not a true “population-based” sample and therefore may not represent the true distribution of COPD severity in the general population. However, we do not believe the inclusion or exclusion criteria biased the population in any significant way as exclusions were primarily focused on concomitant respiratory disorders, life threatening conditions and prior chest surgery. It is possible that reported therapies may be biased according to prescribing patterns at academic centers. However, subjects were recruited from multiple centers in the US not only from

within the participating clinical centers but also from general community advertising. Furthermore, subjects are roughly split with approximately half of the cohort GOLD I-II and the other half GOLD III-IV which makes this cohort ideal for examining the GOLD 2011 classification schema. COPDGene is also one of the largest COPD cohorts with the detailed type of information available needed to stratify patients via the GOLD 2011 classification system and examine prospective outcomes. Another advantage of this cohort is its relatively recent recruitment so as to reflect current prescribing practices. The SGRQ and CAT are not identical. However, the CAT and SGRQ show a very stable relationship across the scaling range¹⁰ and a high degree of correlation, $r=0.84$ in a primary care population of COPD patients in seven European countries⁹. We also acknowledge that the GOLD 2011 classification system is intended to assess risk for exacerbations, hospitalizations and death. Included here are longitudinal data regarding total and hospitalized exacerbations but not mortality data which was not available at the time of this analysis. Additionally, prospective data on exacerbation rates was available in 83% of subjects which could result in either an under or over estimation of actual exacerbation rates.

In summary, the GOLD 2011 classification system identifies COPD subcategories that differ in disease severity assessed by lung function, symptoms and exacerbation frequency. Importantly, we demonstrate that COPD populations indeed are very heterogeneous with poor correlation between lung function, symptoms and exacerbation frequency confirming the need for a classification system based on more than lung function alone. Indeed it is a significant strength of this classification system in that it challenges health care providers to think about their COPD patients in a more “multidimensional” way. However, we also show that the choice of symptom measure can significantly alter category assignment which has implications for the practical application of the GOLD classification system. We also demonstrate the difficulty of using more than one “risk” stratifier as exacerbation history and FEV₁ do not behave identically in predicting risk. FEV₁ is also problematic for risk stratification as it relates both to symptoms and risk. This demonstrates the difficulties in using this classification system to identify homogenous groups of patients for the purposes of clinical trials or tracking health outcomes in which case limiting the symptom and risk assessment to one metric might improve feasibility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of interest for all authors

In the past three years, Dr Han has participated in advisory boards for Boehringer Ingelheim GmbH, Pfizer, GlaxoSmithKline, Genentech, Novartis, and Medimmune. She has participated on speaker's bureaus for Boehringer Ingelheim GmbH, Pfizer, GlaxoSmithKline, Grifols therapeutics and the National Association for Continuing Education, and WebMD. She has consulted for Novartis and United Biosource Corporation. She has received royalties from UpToDate and ePocrates, Inc.

Dr. Hana Muellerova is an employee of GlaxoSmithKline R&D and own shares and stock options of GlaxoSmithKline Plc.

Dr. Curran-Everett has reported no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

In the past three years, Dr Dransfield has consulted for GlaxoSmithKline and Boehringer Ingelheim GmbH. His institution has received funds to conduct clinical research trials for GlaxoSmithKline and Boehringer Ingelheim GmbH.

In the past three years, Dr. Washko has consulted for Spiration.

Dr. Regan has reported no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

In the past three years, Dr. Bowler has served on the speaker bureaus for Pfizer, Boehringer Ingelheim, Astra Zeneca, and Forest.

Dr. Beaty has reported no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Dr. Hokanson has reported no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

In the past 3 years, Dr. Lynch has served as consultant to several trials in idiopathic pulmonary fibrosis, sponsored by Gilead Inc, Actelion Inc, Johnson and Johnson Inc, and Intermune Inc. He is also a consultant for Perceptive Imaging, and receives research support from Siemens Inc.

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In the past three years, Dr. Anzueto has served on advisory boards relating to COPD-related topics for GlaxoSmithKline; MedImmune, LLC; AstraZeneca; Forest Laboratories, Inc; Bayer Healthcare; Boehringer Ingelheim GmbH; and Dey Pharma. He has served on speaker's bureaus for GlaxoSmithKline; Pfizer Inc; Boehringer Ingelheim GmbH; and Forest Laboratories, Inc. His institution has received funds from for a clinical trial

GlaxoSmithKline, and the National Heart, Lung, and Blood Institute. He has received no royalties. He has served on steering committees for clinical trials supported by Forest Laboratories, Inc; and Boehringer Ingelheim GmbH.

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Dr. Crapo has reported no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Dr. Silverman received grant support and consulting fees from GlaxoSmithKline for studies of COPD genetics. He received honoraria and consulting fees from AstraZeneca, and he received consulting fees from Merck.

Over the past 3 years, Dr Make has participated in advisory boards, speaker bureaus, consultations, and multicenter clinical trials with funding from the National Heart, Lung, and Blood Institute; Abbott Laboratories; Astellas Pharma Inc; AstraZeneca; Boehringer Ingelheim GmbH; Dey Pharma, LP; Embryon Inc; Forest Laboratories, Inc; GlaxoSmithKline; Ikaria; MedImmune;Merck; Nabi Biopharmaceuticals; Nycomed; Novartis Pharmaceuticals Corporation; Pfizer Inc; Respiroics Inc; Merck/Schering-Plough; SeQual Technologies; and Talecris Biotherapeutics, Inc.

Figure 1.
GOLD 2011 classification system.⁵

*GOLD I-IV Classification of Airflow limitation based on FEV1¹ from GOLD executive summary 2006.

Figure 2. Distribution of the SGRQ total score by the mMRC Dyspnea Grade in the COPDGene cohort.

Table 1

Prevalence and of GOLD categories by symptom measure choice (mMRC vs. SGRQ)

n=4,484	mMRC Classification System		CAT (SGRQ) Classification Method	
	C: 7.9% (355)	D: 38.0% (1,703)	C: 4.9% (221)	D: 41.0% (1,837)
Meets FEV ₁ criteria (<50% FEV ₁ predicted)	C1: 5.8% (259)	D1: 24.4% (1,096)	C1: 3.9% (173)	D1: 26.4% (1,182)
Meets Exacerbation criteria (2 COPD exacerbations in past 12 mo)	C2: 1.5% (68)	D2: 5.0% (222)	C2: 0.8% (38)	D2: 5.6% (252)
Meets Exacerbation and FEV ₁ criteria(<50% FEV ₁ predicted and 2 COPD exacerbations in past 12 mo)	C3: 0.6% (28)	D3: 8.6% (385)	C3: 0.2% (10)	D3: 9.0% (403)
Subcategory	A: 33.6% (1,507)	B: 20.5% (919)	A: 29.4% (1,317)	B: 24.8% (1,109)
	mMRC 0-1	mMRC 2	SGRQ <25	SGRQ >25

Table 2

Distribution of baseline SGRQ Total score by mMRC grade

mMRC Grade	COPDGene	
	SGRQ Total score	
	N (%)	Mean (SD)
0	1227 (27%)	14 (13)
1	622 (14%)	26 (13)
2	725 (16%)	39 (14)
3	1156 (26%)	50 (16)
4	740 (17%)	63 (15)

Table 3

Baseline Demographics, Symptoms and Exacerbation Frequency using SGRQ Classification in the COPD Gene cohort split by the GOLD Risk Groups

Parameter	A	B	C1	C2	C3	D1	D2	D3
N	1317 (20)	1109 (25)	173 (4)	38 (1)	10 (0)	1182 (26)	252 (6)	403 (9)
Demographics								
Age	63 (9) 62–63	62 (9) 61–61	66 (8) 65–67	65 (8) 62–68*	65 (5) 62–69*	65 (8) 64–65	61 (9) 60–62	63 (8) 62–63
Gender (Male %)	780 (59%)	582 (53%)	103 (60%)	12 (32%)	6 (60%)	703 (59%)	111 (44%)	212 (53%)
Smoking Pack-years	45 (23) 44–46	54 (30) 52–55	50 (24) 47–54	44 (19) 37–50*	62 (22) 46–77*	57 (29) 55–58	51 (27) 48–58	55 (27) 52–57
Current smoking (%)	664 (50%)	608 (55%)	58 (34%)	8 (21%)	1 (10%)	381 (32%)	112 (28%)	112 (28%)
Body mass index	27 (5) 27–28	29 (6) 29–29	27 (6) 26–27	28 (5) 27–30*	25 (5) 22–29*	27 (6) 27–28	30 (7) 29–31	27 (7) 27–28
BODE	0.4 (0.7) 0.4–0.5	1.9 (1.3) 1.8–2.0	2.7 (1.0) 2.5–2.8	0.8 (1.1) 0.4–1.1*	3.0 (1.2) 2.1–3.9*	4.6 (1.4) 4.5–4.7	2.5 (1.2) 2.3–2.6	5.1 (1.3) 5.0–5.2
Lung function and Exercise Capacity								
FEV ₁ , % predicted	78 (15) 77–79	68 (13) 67–79	41 (7) 40–42	68 (12) 64–72*	40 (7) 35–44*	41 (7) 33–34	65 (11) 64–66	32 (10) 31–33
FEV ₁ /FVC	0.62 (0.1) 0.62–0.62	0.59 (0.1) 0.58–0.59	0.45 (0.1) 0.43–0.46	0.59 (0.1) 0.56–0.61*	0.39 (0.1) 0.35–0.44*	0.40 (0.1) 0.39–0.40	0.58 (0.1) 0.57–0.59	0.38 (0.1) 0.37–0.39
Positive bronchodilator response (>12% or >200 cc)	409 (31%)	392 (35%)	64 (37%)	12 (32%)	3 (30%)	426 (36%)	86 (34%)	153 (38%)
6 minute walk distance (m)	457 (107) 453–464	369 (119) 368–381	396 (104) 386–415	434 (86) 405–461*	387 (79) 331–443*	396 (104) 302–315	351 (124) 349–377	276 (127) 277–300
Symptoms								
SGRQ - Total	11 (8) 10–11	45 (15) 44–46	17 (6) 16–18	17 (7) 14–19*	18 (5) 14–21*	51 (16) 50–52	54 (16) 52–26	60 (15) 58–61
Respiratory Symptoms								
mMRC	0.4 (0.8) 0.4–0.5	2.2 (1.2) 2.1–2.3	0.9 (1.0) 0.7–1.0	0.9 (1.0) 0.6–1.2*	0.7 (1.3) 0–1.6*	2.8 (1.1) 2.8–2.9	2.7 (1.1) 2.6–2.9	3.2 (0.9) 3.1–3.3
Chronic bronchitis (%)	137 (10%)	389 (35%)	25 (14%)	10 (26%)	2 (20%)	333 (28%)	112 (44%)	156 (39%)
Total exacerbation rate in the year prior to enrollment	0.07 (0.26) 0.06–0.08	0.27 (0.44) 0.24–0.29	0.18 (0.39) 0.13–0.24	2.45 (0.80) 2.19–2.71*	2.50 (0.71) 2.00–3.01*	0.35 (0.48) 0.32–0.38	2.90 (1.26) 2.74–3.05	3.10 (1.36) 2.96–3.23

Parameter	A	B	C1	C2	C3	D1	D2	D3
Prospective total annual exacerbation rate (SGRQ)	0.17 (0.60) 0.13–0.20	0.55 (1.4) 0.46–0.64	0.58 (1.7) 0.31–0.84*	0.52 (1.2) 0.08–0.97*	1.39 (2.1) 0.0–3.0*	0.89 (1.9) 0.78–1.0	1.34 (2.2) 1.0–1.6*	1.86 (2.5) 1.6–2.1
Prospective annual severe exacerbation rate (SGRQ)	0.02 (0.12) 0.01–0.03	0.13 (0.44) 0.10–0.16	0.06 (0.20) 0.03–0.09*	0.13 (0.52) 0.0–0.31*	0.11 (0.33) 0.0–0.37*	0.27 (0.79) 0.22–0.32	0.57 (1.6) 0.34–0.79*	0.62 (1.2) 0.49–0.75

GOLD Category explanation: A: low symptoms/low risk; B: high symptoms/low risk; C: low symptoms/high risk; and D: high symptoms/high risk. Groups C and D 1–3 were classified based on the qualifying criteria as follows: patients in C1 or D1 qualified based on airflow limitation, FEV1<50% predicted, only, C2 or D2 qualified based on COPD frequent exacerbation history (2 events per past 12 months), and C3 or D3 qualified based on both, airflow limitation and COPD frequent exacerbations history. The number of reported exacerbations in the year prior to enrollment was used for group assignment. Longitudinal follow-up data was available in 3,723 / 4,484 (83%) of participants. Numbers in parentheses are SDs or percentages. The second entry in each cell represents a 95% confidence interval estimated by traditional normal-theory method and verified by 10,000 bootstrap replications.

* Because of small sample size, the confidence interval may be an unreliable estimate; this is reflected in the relative width of this confidence interval compared to the confidence intervals in other groups.