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CHARACTERISTICS, STABILITY AND OUTCOMES OF THE GOLD 2011 COPD GROUPS IN THE ECLIPSE COHORT

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ABSTRACT

The 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD) classifies patients with COPD into four groups (A to D).

We explored the characteristics, stability and relationship to outcomes of these groups within the ECLIPSE study (n=2101).

Main results showed that: *(1)* these groups differed in several clinical, functional, imaging and biological characteristics in addition to those used for their own definition; *(2)* A and D groups were relatively stable over time, whereas groups B and C showed more temporal variability; *(3)* the risk of exacerbation over 3 years increased progressively from A to D, whereas that of hospitalization and mortality were lowest in A, highest in D and intermediate and similar in B and C, despite the former having milder airflow limitation. The prevalence of comorbidities and persistent systemic inflammation were highest in group B.

The different longitudinal behaviour of group A vs. B and C vs. D (each pair with similar FEV_1 values) supports the GOLD 2011 proposal of assessing COPD patients by more than FEV_1 only. However the assumption that symptoms does not equate to risk appears to be naïve, as groups B and C carry equally poor clinical outcomes, though for different reasons.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease, and the forced expiratory volume in the first second (FEV_1) does not describe this complexity fully [1]. The recently released 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations recognize this limitation and propose a novel multidimensional approach to assess COPD patients that includes the level of symptoms (as assessed by either the modified Medical Research Council (mMRC) score or the COPD Assessment Test (CAT), the FEV_1 value (expressed as percentage of predicted value) and the individual history of previous exacerbations [2]. As a result, COPD patients can now be categorized and treated according to four groups (A, B, C and D) [2].

Very recently, three studies have used existing cohorts of COPD patients to explore different aspects of this new GOLD assessment proposal. Han *et al* used the COPDGene cohort [3] to explore the influence of the instrument used to assess the level of symptoms (mMRC vs. St. George's Respiratory Questionnaire (SGRQ), as a surrogate for CAT) on group assignment and risk of exacerbations during follow-up [4]. Lange *et al* investigated the ability of the GOLD 2011 proposal to predict the clinical course of the disease in two Danish general population cohorts combined [5]. Finally, Soriano *et al* determined the distribution and validity of the four GOLD 2011 groups as predictors of mortality in eleven small Spanish cohorts merged for the analysis [6].

The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) is a large, observational, longitudinal, multicenter, international study that: *(1)* includes a very detailed clinical, functional, imaging, and biological characterization

of COPD patients; and, *(2)* follows them up for three years [1,7]. It offers, therefore, a unique opportunity to reproduce some of these previous analyses and to explore other novel aspects of potential relevance. Specifically, in this study we used the ECLIPSE cohort to: *(1)* compare the 2007 and 2011 GOLD recommendations in terms of patient distribution and assessment of disease severity; *(2)* characterize in detail the four GOLD 2011 groups; *(3)* explore their stability after 3 years of follow-up; and, *(4)* investigate their relationship with clinical relevant outcomes (exacerbations, hospitalizations and mortality), and identify significant risk factors.

METHODS

Study design

The design of the ECLIPSE study (Clinicaltrials.gov identifier NCT00292552; GSK study code SCO104960) has been published previously [7]. Briefly, ECLIPSE is an observational, longitudinal and controlled study that recruited patients mostly from those attending the outpatient clinics of secondary or tertiary care hospitals and, occasionally, from primary care. After a baseline visit, participants were evaluated at 3 months, 6 months and then every 6 months for 3 years. ECLIPSE complies with the Declaration of Helsinki and Good Clinical Practice Guidelines, and has been approved by the ethics committees of the participating centres. All participants provided written informed consent.

Population

The original ECLIPSE cohort included 2,164 patients with COPD, as previously published [1]. Since the mMRC dyspnoea score was missing in 62 patients and 1 patient had an unknown GOLD stage, the present analysis includes 2,101 GOLD I-IV patients

(97% of the original ECLIPSE cohort) with full GOLD 2011 data. These 2,101 patients were categorized into one of four groups (A, B, C or D) according to the GOLD 2011 recommendations [2] using the mMRC score (the CAT had not been published [8] when the ECLIPSE study was designed [7]) and the FEV_1 value, both measured at recruitment, as well as the number of exacerbations retrospectively recorded from the year before inclusion in ECLIPSE.

Measurements

The methodology used in ECLIPSE has also been reported in detail elsewhere [1,7]. We used standardized questionnaires to record dyspnea (modified Medical Research Questionnaire (mMRC)), comorbidities ((ATS-DLD-78 questionnaire), health-status (St. George's Respiratory Questionnaire for COPD patients (SGRQ-C)) and depression (Center for Epidemiological Studies Depression Scale (CES-D)) [1,7]. Nutritional status was assessed by the body mass (BMI) and fat-free mass indexes (FFMI) by bioelectrical impedance [7]. COPD exacerbations requiring treatment with antibiotics, oral corticosteroids and/or hospitalization in the year prior to the study (and during follow-up) were also recorded. Spirometry and the 6 minute walking distance (6MWD) were performed according to international guidelines [9,10]. Spirometric reference values were those of the European Community for Coal and Steel (ECCS) [11]. The BODE index was calculated according to Celli et al [12]. All subjects underwent a low-dose computed tomography (CT) scan of the chest acquired using multi-detector-row CT scanners (GE Healthcare or Siemens Healthcare), as described elsewhere [1]. Hospitalizations and all-cause mortality were recorded during 3-years follow up [13,14]. Finally, the annual rate of FEV_1 decline in each patient [15] and the proportion of

patients with persistent systemic inflammation at baseline [14] were calculated as reported previously and included in the current analysis.

Statistical analysis

Results are shown as mean (SD) or proportion, as appropriate. Jonckheere-Terpstra tests were used to assess differences in subject characteristics among groups with ordering of A ≤ B ≤C ≤ D [16]. Kaplan–Meier curves were constructed to describe the occurrence of exacerbations, hospitalizations and all-cause mortality over the study period for both the 2007 [17] and 2011 GOLD [2] classifications. Concordance probabilities and their associated 95% confidence intervals were calculated for Cox regression models for exacerbations, hospitalizations and all-cause mortality to evaluate the predictive accuracy of the 2007 and 2011 GOLD classifications [18]. A Cox proportional hazards regression model was used to identify factors associated with increased risk of mortality and hospitalization, A p value lower than 0.05 (two sided) was considered statistically significant.

RESULTS

Patient distribution and assessment of disease severity by the 2007 and 2011 GOLD recommendations

Figure 1 shows the distribution of the COPD patients included in the analysis according to the 2007 (panel A) and 2011 (panel B) GOLD recommendations. The latter resulted in a right-ward shift of the distribution indicating that more patients were being classified in more severe groups. The mean (±SD) 2007 GOLD stage was not different between groups A (2.0±0.0) and B (2.0±0.1), and only slightly worse (albeit statistically

significantly so; $p<0.001$) between groups C (3.0±0.5) and D (3.2±0.6). Figure 1 (panel C) also shows the cumulative distribution of the four GOLD 2011 groups within each GOLD 2007 stage. GOLD II includes a large proportion of group A (54%) and B (32%) patients but also some group C (7%) and D patients (8%). Since, by definition, GOLD stage II patients must have an FEV_1 ≥50% predicted [17], these latter two groups were classified as high risk groups (C or D) exclusively because of their past exacerbation history (≥2/yr.). On the other hand, also by definition, GOLD stages III and IV cannot include group A or B patients, whose FEV_1 must be ≥50% of reference [2]. There were more group D patients in GOLD stage IV than GOLD stage III (Figure 1, panel C). The frequency distribution of these four groups was not different in males and females (Table 1E).

Characterization of the 2011 GOLD groups

The application of the GOLD 2011 assessment criteria resulted in the expected differences in the mMRC scores, FEV_1 and exacerbation rates between the four groups (Table 1). In addition, these four groups differed also in many of the other characteristics studied (Tables 1 and 2E). It is of note that some variables were particularly abnormal in the two high symptoms groups (B and D; SGRQ-C and CES-scores, many comorbid conditions, exercise capacity and most inflammatory biomarkers), whereas other were mostly abnormal in the two high risk groups (C and D; amount of emphysema present and arterial oxygenation saturation) (Tables 1 and 2E). Finally, of note, age, gender, cumulative smoking exposure, FEV_1 reversibility and the annual rate of FEV_1 decline were either not different between groups or differences were of unlikely clinical relevance (Tables 1 and 2E).

As in two previous studies [4,5], we stratified the C and D groups further according to the specific criteria that determined the inclusion of patients in these high risk groups (FEV_1<50% ref (C1 or D1), exacerbation history≥2 / yr. (C2 or D2) or both (C3 or D3)). An FEV_1 <50% of reference alone was the most frequent reason to classify a patient as high risk, in either the C or D groups (70% and 63% of cases, respectively), whereas the presence of frequent exacerbations alone was responsible for a much lower proportion of patients (13% and 9%, respectively); the remaining patients (18% and 28%, respectively) were classified as C or D patients because the presence of both low FEV_1 and frequent exacerbations. Tables 3E and 4E present the main characteristics of these three C and D subgroups. By definition, exacerbation frequency was particularly high in C2/D2 and C3/D3.

Temporal stability of the GOLD 2011 groups at 3 years follow-up

Figure 2 presents the distribution of the four GOLD 2011 groups both at recruitment and 3 years later. It is important to note, however, that not all patients studied at recruitment contributed data at 3 years of follow up due to a variety of reasons that include death, drop-out, lost for follow-up and/or missing data. This effect was less marked in group A, worse in group D and intermediate in groups B and C. With this caveat in mind, it is interesting to see that the relative majority of A and D patients do remain in their original classification, whereas B and C patients have greater temporal variability (Figure 2). B patients either remained in the same category (B), improved (A) or deteriorated (D) in roughly similar proportions. By contrast C patients, either remained stable (C) or deteriorated (D) and only a relatively small fraction improved (B or A). Finally, it is of note that the proportion of patients that moved to group A from B, C or D was lowest in D, intermediate in C and largest in B (Figure 2).

Relationship with long-term outcomes: comparison of the GOLD 2007 and 2011 recommendations

Figure 3 presents Kaplan–Meier curves that describe the occurrence of exacerbations (left), hospitalizations (middle) and all-cause mortality (right) over the study period for GOLD 2007 (all patients; top panels), GOLD 2011 (all patients; middle panels) and GOLD 2011 including only patients with FEV_1<50% of predicted (GOLD II) (bottom panels). Within GOLD 2007 (top panels), each of the pairwise comparisons are significantly different for exacerbations, hospitalizations ($p<0.001$) and all-cause mortality ($p\leq0.002$). Similarly, within GOLD 2011 (all patients; middle panels), each of the pairwise comparisons are also significantly different for exacerbations ($p<0.001$) but not for hospitalizations or mortality, which were different in A and D ($p\leq0.010$) but similar in B and C patients, despite group B having better lung function and fewer exacerbations; yet, group B also had, at baseline, the highest prevalence of comorbidities (Table 1), particularly cardiac comorbidities (Table 2E), and of patients with persistent systemic inflammation (Figure 4), defined as we described previously [14].

Compared with the GOLD 2007 classification, GOLD 2011 had a higher concordance probability [95% CI] for predicting exacerbations (0.591 [0.577, 0.605] vs. 0.570 [0.558, 0.583], p=0.003) and hospitalizations (0.659 [0.640, 0.679] vs. 0.628 [0.610, 0.646], p=0.001); both classifications were similar for the prediction of all-cause mortality (0.596 [0.562, 0.630] vs. 0.614 [0.576, 0.653], p=0.32).

Because there is limited information in the ECLIPSE database on specific causes of death [1,7], we used a Cox proportional hazards regression model to identify factors associated with increased risk of mortality. These included more severe airflow limitation, higher age, lower BMI, higher FFMI, increased number of comorbidities, and lower exercise capacity (Table 2). Interestingly, GOLD B patients had less airflow limitation and higher BMI than GOLD C patients, but were older, had a higher FFMI, more co-morbidities, and poorer exercise capacity (Table 1). These differences may contribute to their similar mortality during follow-up (Figure 3). A similar set of covariates (FEV1 % predicted, age, BMI, number of comorbidities, prior exacerbation history, arterial O_2 saturation and dyspnoea) were associated with increased risk of hospitalization (Table 2). For each of these covariates, differences were also noted between GOLD B and GOLD C patients (Table 1).

Two final aspects of our analysis deserved comment. First, there were no significant differences between genders across the four groups for mortality or hospitalizatons during follow up (Table 1E) but females had a higher exacerbation rate than males ($p \leq 0.017$). Second, if only GOLD 2007 stage II patients (FEV_1>50% of reference) are considered (Figure 1, panel C), the GOLD 2011 proposal lacks discriminant power to predict exacerbations in C2 and D2 patients, the risk of hospitalization is similar and intermediate in C2 and B patients and, interestingly, mortality during follow-up was zero in C2 patients (Figure 3, bottom panels).

DISCUSSION

The 2011 GOLD recommendations have proposed a novel, multi-dimensional strategy to assess disease severity and guide therapy in COPD [2]. Because this proposal was

mostly based on expert opinion [2], several recent studies have used existing COPD cohorts to test it [4-6]. Our study confirms some of their results and extends them by presenting novel aspects not previously explored.

Previous findings

Our results reproduce and support five previous observations: (1) in keeping with Lange et al [5] we found that the new 2011 GOLD classification assesses disease severity differently from the previous 2007 proposal since more individuals are categorized in the more severe group (Figure 1, panels A and B). This is not surprising if the multi-dimensional nature of the 2011 GOLD proposal is considered [2]; (2) the prevalence of the four GOLD 2011 groups in our study (Figure 1, panel B) was similar to that reported in previous COPD cohorts recruited from hospital clinics [4,6] but clearly different from that described in COPD patients identified in the general population, where group A clearly predominates [5]; (3) also in agreement with previous reports [4,5] we found that a low FEV1 (<50% ref.) was the main reason for classifying patients as high risk (C and D groups); (4) we reproduced previous observations (Figure 3, middle panel) indicating that the new GOLD 2011 assessment proposal predicts future exacerbations appropriately [4,5]. Likewise, in keeping with Lange et al [5], we observed that mortality was similar in groups B and C (Figure 4), despite the former having, by definition, better lung function and fewer exacerbations [2]. We think that this is a clear example of how the new GOLD 2011 assessment proposal goes beyond FEV1 and identifies a group of patients who, despite the presence of moderate airflow limitation are at high risk of mortality. Soriano et al reported a similar observation at 3 but not at 10 years of follow-up [6], raising the possibility of different causes of death at different time points of follow-up. The specific causes of death were not investigated by

Soriano et al [6], but Lange et al reported that B patients often die of cardiovascular disease and cancer [5]. In keeping with this observation, we also found that B patients showed the highest prevalence of comorbidities and included more patients with persistent systemic inflammation (Figure 4, Table 1). The former is known to have a direct and significant impact on survival in COPD [19] and the latter has been recently shown to increase mortality six-fold irrespective of the severity of the pulmonary abnormalities present [14]. These observations may have clinical implications for the practitioner, since B patients appear to be a unique group that deserves special attention in order to understand the origin of their greater symptoms, which are likely to relate to the presence of comorbidities, which may occur in patients with moderate airflow limitation [1], and need to be actively looked for and treated adequately if present [2]; and, finally, *(5)* the observation that despite having frequent exacerbations and requiring frequent hospitalizations, C2 patients have a mortality of zero during follow-up (Figure 3) is also of clinical interest and in keeping with the observations by Lange *et al* [5].

Novel observations

Our study extends previous reports [4-6] by providing potentially relevant information on six aspects not investigated before: *(1)* we found that the four GOLD 2011 groups differed in many clinical, functional, imaging and biological characteristics in addition to those used for their categorization (Tables 1 and 2E). Interestingly, some of them (comorbidities, systemic inflammation) are more prevalent in the two high symptom groups (B and D), whereas others (emphysema, low arterial oxygen saturation) are more prevalent in the two high risk groups (C and D) (Tables 1 and 2E). Although both Han *et al* [4] and Lange *et al* [5] identified some of these differences, the level of characterization of the participants in ECLIPSE is much more detailed so, this

information constitutes an important repository of data (Tables 1, 2E, 3E and 4E) of potential use for a better understanding of the disease and for the design of future studies; *(2)* our analysis is the first to investigate the temporal stability of the four GOLD 2011 groups. We observed that relative majority of A and D patients do actually remain in their original classification, whereas B and C patients present higher temporal variability (Figure 2). These changes can be due to either disease progression or the beneficial effect of therapy but, in any case, this observation provides evidence of the degree of heterogeneity of the natural history of the disease and may highlight a potential window of opportunity for therapeutic intervention; *(3)* also not explored previously [4-6], we found that the GOLD 2011 assessment proposal does not separate the COPD cohort into groups that differ in their rate of FEV_1 decline (Table 1). This suggests that further segmentation of the COPD population beyond that proposed by GOLD 2011 may be required to fully describe COPD heterogeneity since several recent studies [20,21], including an analysis of the ECLIPSE cohort [15], have clearly shown that the rate of FEV_1 decline varies among COPD patients; *(4)* no previous study has investigated the relationship of the four GOLD 2011 groups with hospitalizations during follow-up. We found that, similarly to mortality, hospitalizations were less prevalent in A, most in D and intermediate and similar in the B and C groups (Figure 3). As in the case of mortality discussed above, this observation emphasizes a sometimes overlooked fact; i.e., that patients with COPD may require hospitalization (and/or die) for reasons not directly related to COPD (comorbidities). Because they are amenable to therapy [22], this observation supports the emphasis made by the GOLD 2011 document on the importance of actively looking for, and treating adequately if present, the comorbidities known to frequently occur in COPD patients [2]; *(5)* since ECLIPSE does not have information on specific causes of death, we explored factors associated with increased

risk of mortality (and hospitalizations) using a Cox proportional hazards regression model. Interestingly the identified risk factors were similar for mortality and hospitalizations (Table 2). The fact that they were distributed relatively evenly between B and C patients (Tables 1 and 2E) may in part explain the relatively similar outcomes exhibited by these two groups despite their different severities of airflow limitation and/or past history of exacerbations, and may help clinicians to assess the risk of individual patients; and, finally, *(6)* we explored for the first time potential gender differences among GOLD 2011 groups. We found that the frequency distribution was not different in males and females (Table 1E). Furthermore, we observed that there were no significant gender differences for mortality or hospitalizations although, interestingly, females had a higher ($p \leq 0.017$) exacerbation rate during follow-up than males (Table 1E);

Potential limitations

The following potential limitations of our study deserve comment: *(1)* like all previous studies [4-6], our analysis took advantage of an existing cohort assembled for different purposes, so it might not mirror the population of COPD patients at large; *(2)* because patients enrolled in ECLIPSE were mostly recruited from hospital clinics and were treated according to the attending physician, our results may not be directly generalizable to untreated patients or patients with milder disease (GOLD stage I). However, it is of interest that Lange *et al.* reported similar observations in patients recruited from the general population with a skewed distribution towards milder disease (77% classified in the A group) [5]; *(3)* because of the inclusion criteria used in ECLIPSE (age 40–75 yrs., baseline post-bronchodilator FEV1 <80% of the predicted value, baseline post-bronchodilator FEV1/ FVC ≤ 0.7 and a smoking history ≥10 pack-

yrs. [7]), it is possible that a small fraction of A and B patients analysed here may be above the lower limit of the normal. Yet, all of them were diagnosed of COPD by their attending physicians considering their exposure to risk factors and current clinical symptomatology; and, finally, *(4)* co-morbidities were self-reported and we lack information on specific causes of death, so some of our observations and interpretations require prospective validation in future studies.

Conclusions

The different longitudinal behaviour of group A vs. B, and C vs. D (both pairs with similar FEV_1 values) supports the GOLD 2011 proposal of assessing COPD patients by more than the degree of airflow limitation only. However the assumption that symptoms does not equate to risk appears to be naïve, as groups B and C carry equally poor clinical outcomes though for different reasons. The latter may explain why group B patients are those most likely to switch grouping over time.

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Table 1: Mean (SD), median [IQR], or proportion of the main characteristics and outcomes of the four groups of patients as per the 2011 GOLD recommendations [2].

	GOLD 2011 groups				
Distribution	**Group A**	**Group B**	**Group C**	**Group D**	**p value**
N	495	293	483	830	
Percent	24%	14%	23%	40%	
GOLD 2011 assessment variables					
mMRC dyspnoea score	0.6 (0.5)	2.3 (0.6)	0.8 (0.4)	2.6 (0.7)	<0.001
FEV_1 % predicted	64.2 (8.1)	61.6 (8.2)	42.2 (11.5)	37.2 (11.2)	<0.001
Exacerbations previous 12 months	0.2 (0.4)	0.3 (0.5)	1.0 (1.4)	1.3 (1.4)	<0.001
Demographics					
Age, years	63.2 (7.2)	64.1 (7.3)	62.9 (7.2)	63.6 (6.9)	0.078
Female, %	191 (39%)	106 (36%)	149 (31%)	280 (34%)	0.07
BMI, kg/m^2	26.7 (4.8)	28.5 (6.1)	25.2 (4.9)	26.5 (6.1)	<0.001
FFMI, kg/m^2	17.3 (2.5)	18.0 (3.5)	16.7 (2.5)	17.1 (2.9)	<0.001
Smoking, pack-years	48.0 (29.4)	47.5 (25.8)	45.2 (23.2)	51.1 (27.7)	<0.001
Current smoker, %	188 (38%)	101 (34%)	207 (43%)	267 (32%)	0.001
Symptoms					
Chronic bronchitis, %	131 (26%)	104 (35%)	182 (38%)	318 (38%)	<0.001
SGRQ-C Total score	31.9 (17.3)	55.3 (15.5)	44.6 (16.8)	62.2 (15.6)	<0.001
CESD Total score	8.3 (8.0)	13.8 (9.4)	9.5 (8.2)	13.5 (9.7)	<0.001
Self-reported comorbidities					
With any comorbidity, %	383 (77%)	248 (85%)	350 (72%)	690 (83%)	<0.001
Number of comorbidities	2.0 (1.7)	2.8 (2.2)	1.7 (1.7)	2.3 (1.9)	<0.001
Physiology					
FEV_1 % reversibility	11.4 (13.2)	11.8 (12.9)	10.3 (13.5)	10.2 (14.5)	0.035
SaO2, %	95.7 (2.1)	95.1 (2.5)	94.4 (3.2)	93.7 (3.2)	<0.001
6MWD, m	440 (106)	360 (101)	408 (106)	307 (114)	<0.001
BODE Index	0.8 (0.8)	2.7 (1.2)	2.6 (1.2)	5.1 (1.6)	<0.001
Imaging					
%LAA, -950HU	11.8 (9.7)	12.5 (9.9)	18.9 (11.5)	22.5 (12.8)	<0.001
Outcomes during follow-up (3 yrs)					
ECOPD, per year	0.6 (0.8)	0.9 (1.0)	1.3 (1.4)	1.7 (1.7)	<0.001
>=1 Hospitalization, %	56 (11%)	71 (25%)	143 (30%)	378 (46%)	<0.001
Mortality rate, %	22 (4%)	28 (10%)	41 (8%)	114 (14%)	<0.001
Mortality rate per 100 patient-years	1.6 (7.4)	3.7 (11.5)	3.2 (10.5)	5.5 (13.7)	<0.001
Rate of annual FEV_1 decline, ml/yr.	-33.4	-38.0	-30.2	-31.9	0.157

mMRC, dyspnea score according to the modified Medical Research Council questionnaire; FEV_1, expired volume of gas in the 1st second of a forced spirometry; BMI, body mass index; FFMI, fat-free mass index; SGRQ-C, Saint George Respiratory Questionnaire for COPD patients; CESD, Center for Epidemiological Studies Depression Scale; SaO_2, arterial oxygen saturation; 6MWD, 6-minute walking distance test; BODE index, Body mass index, Airflow Obstruction, Dyspnea and Exercise index; % LAA, percentage of low attenuation areas (i.e., emphysema) in the computed tomography: ECOPD, exacerbation of COPD.

Table 2. Cox Proportional Hazards Regression analysis for all-cause mortality and hospitalizations during follow-up. For further explanations, see text.

Independent Variable	Hazard Ratio Estimate (95% CI)	p-value
Mortality		
FEV_1 % predicted	0.982 (0.969,0.996)	0.011
Age, years	1.052 (1.021,1.085)	<0.001
BMI, kg/m^2	0.931 (0.882,0.983)	0.01
FFMI, kg/m^2	1.146 (1.036,1.267)	0.008
Number of comorbidities	1.100 (1.001,1.210)	0.048
6MWD, m	0.997 (0.996,0.999)	0.002
Hospitalizations		
mMRC dyspnoea score	1.246 (1.119,1.387)	<0.001
FEV_1 % predicted	0.974 (0.966,0.982)	<0.001
Exacerbations previous 12	1.195 (1.123,1.270)	<0.001
Age, years	1.021 (1.005,1.038)	0.01
BMI, kg/m^2	0.979 (0.960,0.999)	0.04
Hypertension	0.669 (0.526,0.851)	0.001
Angina	0.565 (0.371,0.858)	0.007
Osteoarthritis	0.695 (0.489,0.987)	0.042
Diabetes	0.604 (0.392,0.932)	0.023
Depression requiring	0.657 (0.473,0.912)	0.012
Number of comorbidities	1.209 (1.113,1.314)	<0.001
SaO2, %	0.929 (0.902,0.956)	<0.001

BMI, body mass index; FFMI, fat-free mass index; 6MWD, six-minute walking distance; mMRC, modified Medical Resarch Council; SaO2, arterial oxygen saturation.

FIGURE LEGENDS

Figure 1. Frequency distribution of the COPD patients studied here according to the 2007 (panel A*)* or 2011 GOLD recommendations (panel B). Panel C shows the cumulative distribution of the four patient groups of GOLD 2011 within each GOLD 2007 stage. For further explanations, see text.

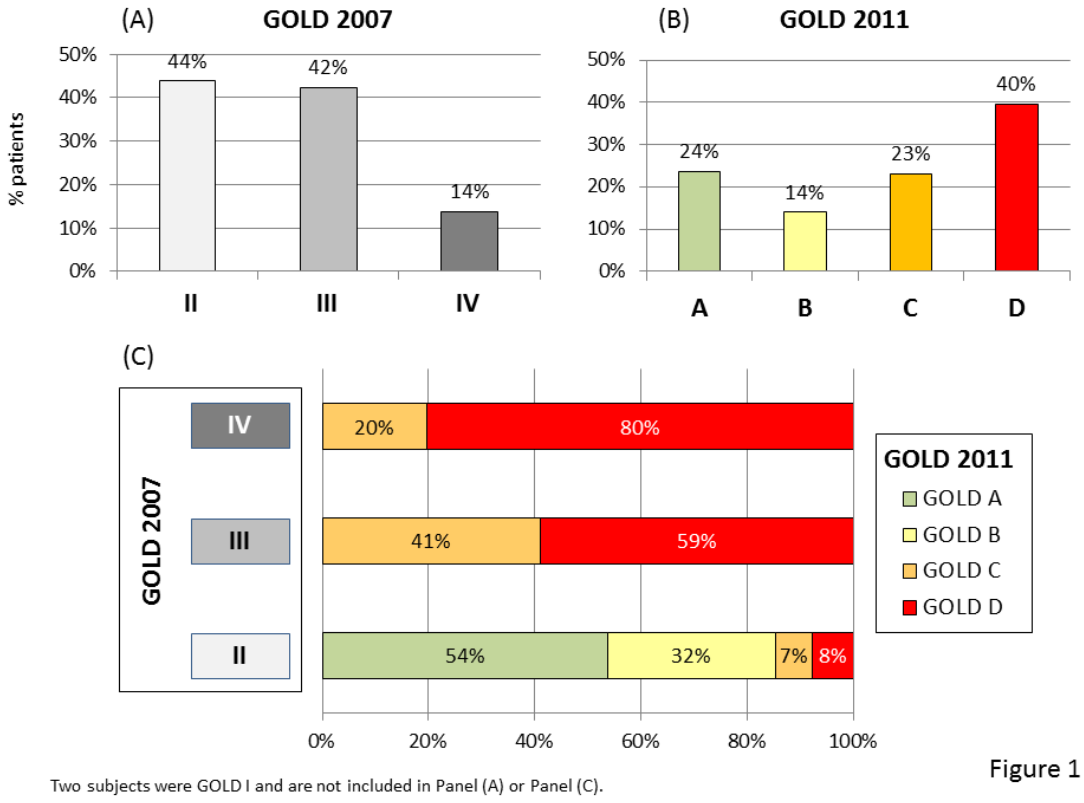


Figure 1

Two subjects were GOLD I and are not included in Panel (A) or Panel (C).

Figure 2. Temporal variation of the four 2011 GOLD groups, at recruitment and 3 years later. Boxes with percentages indicate the proportion of baseline patients available for examination at 3 years follow-up. For further explanations, see text.

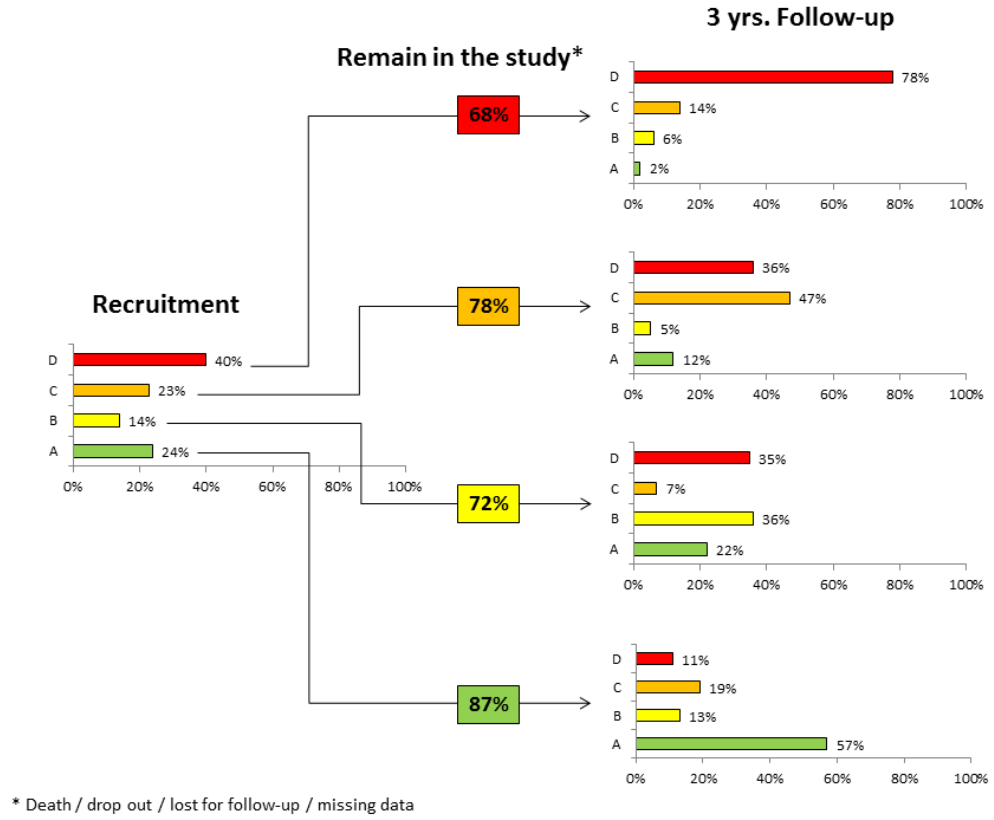


Figure 2

Figure 3. Kaplan–Meier curves for exacerbations (left), hospitalizations during follow-up (middle) and all-cause mortality (right) for the GOLD 2007 (all patients; top panel), GOLD 2011 (all patients; middle panels) and GOLD 2011 (only patients with GOLD II (FEV_1 ≥50% ref; bottom panels) recommendations. For further explanations, see text.

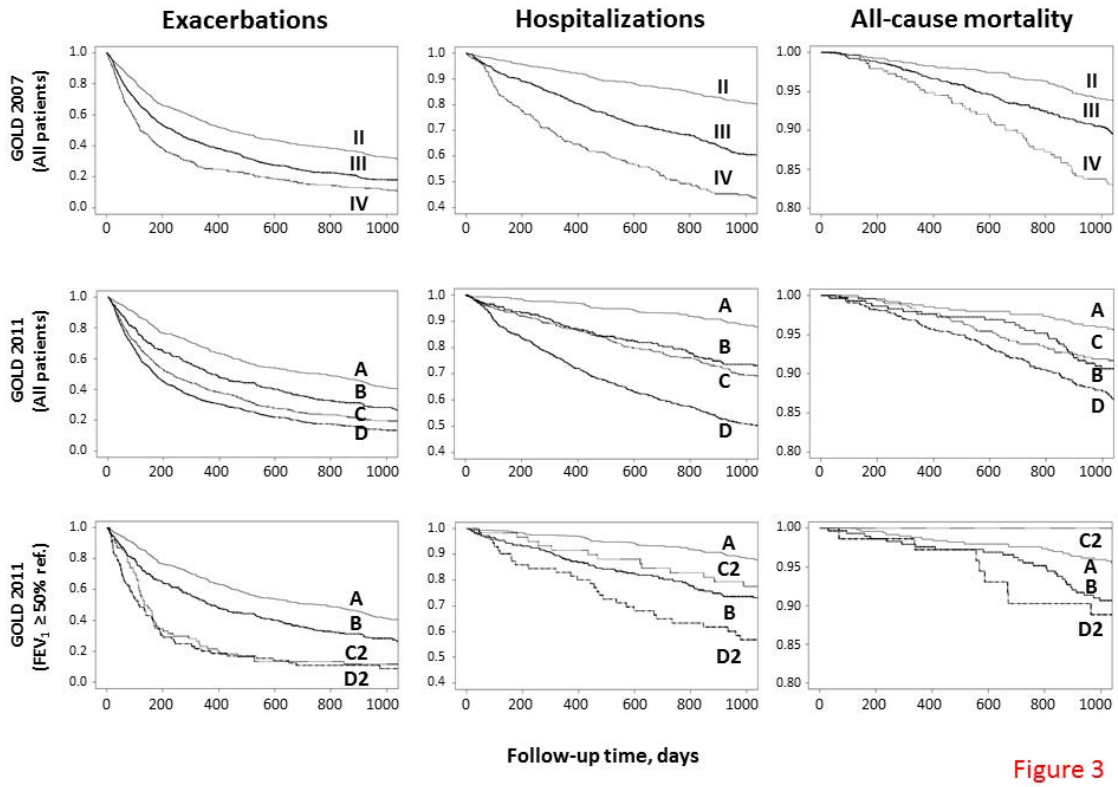
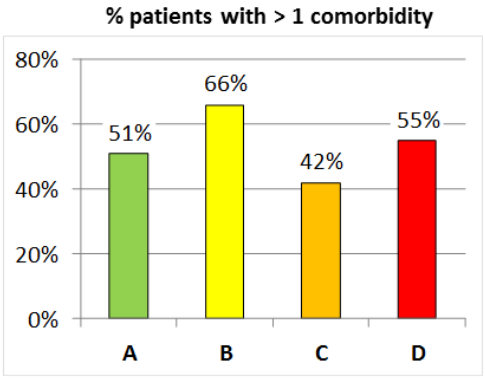
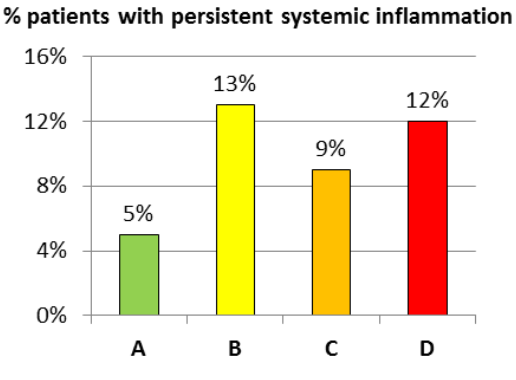


Figure 3

Figure 4. Percentage of patients with at least one self-reported comorbidity (left) or persistent systemic inflammation (right), as described in Ref. [14], in the four GOLD 2011 patient groups. It is of note that both were highest in B patients. For further explanations, see text



All comparisons p<0.05 except for A versus D



All comparisons p<0.05 except for B versus D

Figure 4

APPENDIX 1

AUTHORS' CONTRIBUTIONS

AA was a study investigator, developed the study protocol, served on the scientific committee, interpreted study data, developed the first draft of the manuscript, contributed to and reviewed drafts of the manuscript, and approved the final version of the manuscript; **LDE** developed the study protocol, served on the steering committee, performed statistical analysis and interpreted data, contributed to and reviewed drafts of the manuscript, and approved the final version of the manuscript; **BC** was a study investigator, developed the study protocol, served on the scientific committee, interpreted study data, contributed to and reviewed drafts of the manuscript, and approved the final version of the manuscript; **WM** was a study investigator, developed the study protocol, served on the steering and scientific (Chair) committees, interpreted study data, contributed to and reviewed drafts of the manuscript, and approved the final version of the manuscript; **PMAC** developed the study protocol, served on the scientific committee, interpreted study data, contributed to and reviewed drafts of the manuscript, and approved the final version of the manuscript; **HM** developed the study protocol, interpreted study data, contributed to and reviewed drafts of the manuscript, and approved the final version of the manuscript; **DAL** developed the study protocol, served on the steering committee, interpreted study data, contributed to and reviewed drafts of the manuscript, and approved the final version of the manuscript; **EW** served on the scientific committee, developed the study protocol interpreted study data, contributed to and reviewed drafts of the manuscript, and approved the final version of the manuscript; **PB** was a study investigator, developed the study protocol, served on the steering committee, interpreted study data, contributed to and reviewed drafts of the manuscript,

and approved the final version of the manuscript; **SR** was a study investigator, developed the study protocol, served on the scientific committee, interpreted study data, contributed to and reviewed drafts of the manuscript, and approved the final version of the manuscript; **CC** developed the study protocol, served on the steering and scientific committees, interpreted study data, contributed to and reviewed drafts of the manuscript, and approved the final version of the manuscript; **BEM** interpreted data, contributed to and reviewed drafts of the manuscript, and approved the final version of the manuscript; **HOC** developed the study protocol, served on the steering committee, interpreted study data, contributed to and reviewed drafts of the manuscript, and approved the final version of the manuscript; **JCY** developed the study protocol, served on the steering and scientific committees, interpreted study data, contributed to and reviewed drafts of the manuscript, and approved the final version of the manuscript; **RT-S** developed the study protocol, served on the steering and scientific committees, interpreted study data, contributed to and reviewed drafts of the manuscript, and approved the final version of the manuscript; **JV** was a study investigator, developed the study protocol, served on the steering committee, interpreted study data, contributed to and reviewed drafts of the manuscript, and approved the final version of the manuscript. The study sponsor did not place any restrictions with regard to statements made in the final version of the article.

ROLE OF THE FUNDING SOURCE

The study was sponsored by GlaxoSmithKline. A Steering Committee and a Scientific Committee comprising in total eleven academics and six representatives of the sponsor developed the original study design and concept, the plan for the current analyses, approved the statistical plan, had full access to the data, and was responsible for

decisions with regard to publication. The study sponsor did not place any restrictions with regard to statements made in the final paper. Two authors of the current paper (AA and JV) are members of the Scientific Committee of GOLD and, as such, co-authors of the new GOLD 2011 recommendations (www.goldcopd.org). The current analysis was conducted after these recommendations were made public in November 2011.

CONFLICTS OF INTERESTS

AA has received reimbursements, fees, or funding from GlaxoSmithKline, Almirall, AstraZeneca, Boheringer Ingelheim, Roche, Nycomed, Novartis and Procter & Gamble; **LDE** is an employee and shareholder of GlaxoSmithKline, the sponsor of ECLIPSE; **BC** has received grants to the pulmonary division he works in to complete research studies from GlaxoSmithKline, Boehringer Ingelheim, Forrest Medical, AstraZeneca and Aeris; has served advisory boards for GlaxoSmithKline, Boehringer Ingelheim, Almirall, AstraZeneca, Aeris and Deep Breeze; has received speaker fees from GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca, Almirall and Esteve; does not have shares or interest in any company. Neither does the family; has not received tobacco money nor has stocks in any tobacco-related companies; **WM** has been reimbursed for travel by GlaxoSmithKline, Zambon, AstraZeneca, Boehringer Ingelheim, Pfizer and Micromet for attending conferences; has received honoraria from GlaxoSmithKline and AstraZeneca for participating as a speaker in scientific meetings; serves on advisory boards for GlaxoSmithKline, Pfizer, Almirall, Amgen, Bayer and Micromet; serves as a consultant for Pfizer and SMB Pharmaceuticals; **PMAC** has received consulting fees from AstraZeneca, GlaxoSmithKline, Nycomed and Pfizer; speaking fees from GlaxoSmithKline and Nycomed; and grant support from Boehringer Ingelheim and GlaxoSmithKline; **HM** is an employee and shareholder of

GlaxoSmithKline, the sponsor of ECLIPSE; **DAL** has received grant funding, honoraria and travel expenses from GlaxoSmithKline and serves as Chair of the Respiratory Therapy Area Board of GlaxoSmithKline; **EW** serves on an advisory board for Nycomed; has received lecture fees from GlaxoSmithKline, AstraZeneca and Novartis; has received research grants from GlaxoSmithKline and AstraZeneca; **PB** has received lecture fees from AstraZeneca, GlaxoSmithKline and NycoMed; has participated in clinical research studies sponsored by GlaxoSmithKline, Pfizer and Boehringer Ingelheim; **SR** has received industry-sponsored grants from: AstraZeneca, Biomarck, Centocor, Mpex, Nabi, Novartis, Otsuka; SR has consulted or participated in advisory boards for: Able Associates, Adelphia Research, Almirall/Prescott, APT Pharma/Britnall, Aradigm, AstraZeneca, Boehringer Ingelheim, Chiesi, CommonHealth, Consult Complete, COPDForum, DataMonitor, Decision Resources, Defined Health, Dey, Dunn Group, Eaton Associates, Equinox, Gerson, GlaxoSmithKline, Infomed, KOL Connection, M. Pankove, MedaCorp, MDRx Financial, Mpex, Novartis, Nycomed, Oriel Therapeutics, Otsuka, Pennside Partners, Pfizer (Varenicline), PharmaVentures, Pharmaxis, Price Waterhouse, Propagate, Pulmatrix, Reckner Associates, Recruiting Resources, Roche, Schlesinger Medical, Scimed, Sudler and Hennessey, TargeGen, Theravance, UBC, Uptake Medical, VantagePoint Management. SR has given lectures for: American Thoracic Society, AstraZeneca, Boehringer Ingelheim, California Allergy Society, Creative Educational Concept, France Foundation, Information TV, Network for Continuing Ed, Novartis, Pfizer, SOMA; **CC** is an employee and shareholder of GlaxoSmithKline, the sponsor of ECLIPSE; **BEM** is an employee and shareholder of GlaxoSmithKline, the sponsor of ECLIPSE; **HOC** has received an honorarium for serving on the steering committee for the ECLIPSE project for GlaxoSmithKline. In addition **HOC** was the co-investigator on

two multicentre studies sponsored by GlaxoSmithKline and has received travel expenses to attend meetings related to the project. **HOC** has three contract service agreements with GlaxoSmithKline to quantify the CT scans in subjects with COPD and a service agreement with SpirationInc to measure changes in lung volume in subjects with severe emphysema **HOC** is the co-investigator (D Sin PI) on a Canadian Institutes of Health – Industry (Wyeth) partnership grant. **HOC** has received a fee for speaking at a conference and related travel expenses from AstraZeneca (Australia); **JCY** is an employee and shareholder of GlaxoSmithKline, the sponsor of ECLIPSE; **RT-S** is an employee and shareholder of GlaxoSmithKline, the sponsor of ECLIPSE; **JV** has received fees for advising and/or presenting from GlaxoSmithKline, AstraZeneca, Pfizer, Bioxydyn, Boehringer Ingelheim, Nycomed, Hoffmann-La Roche, Talecris, Kamada and Sounds Biotech; has received research support from GlaxoSmithKline.

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