Prediction of the Clinical Course of Chronic Obstructive Pulmonary Disease, Using the New GOLD Classification

A Study of the General Population

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***Rationale*: The new Global Initiative for Obstructive Lung Disease (GOLD) stratification of chronic obstructive pulmonary disease (COPD) into categories A, B, C, and D is based on symptoms, level of lung function, and history of exacerbations.**

***Objectives*: To investigate the abilities of this stratification to predict the clinical course of COPD.**

***Methods*: Two similar population studies were performed in an area of Copenhagen including 6,628 individuals with COPD.**

***Measurements and Main Results*: The patients were monitored for an average period of 4.3 years regarding COPD exacerbations, hospital admissions, and mortality. The percentages of individuals experiencing a COPD exacerbation during the first year of observation were 2.2% in group A, 5.8% in group B, 25.1% in group C, and 28.6% in group D. One- and 3-year mortality rates were 0.6 and 3.8%, respectively, in group A, 3.0 and 10.6% in group B, 0.7 and 8.2% in group C, and 3.4 and 20.1% in group D. Groups B and D, characterized by a higher degree of dyspnea than groups A and C, had five to eight times higher mortality from cardiovascular disease and cancer than did groups A and C.**

***Conclusions*: The new stratification performs well by identifying individuals at risk of exacerbations. Surprisingly, subgroup B, characterized by more severe dyspnea, had significantly poorer survival than group C, in spite of a higher FEV_1 level. This subgroup warrants special attention, as the poor prognosis could be caused by cardiovascular disease or cancer, requiring additional assessment and treatment.**

Keywords: COPD; guidelines; prognosis; comorbidities

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The Global Initiative for Obstructive Lung Disease (GOLD) launched the 2011 revision of the strategy document for diagnosis and management of chronic obstructive pulmonary disease (COPD) in December 2011. It is not known how this profound change in the stratification strategy works regarding prediction of the clinical course of COPD.

What This Study Adds to the Field

First, we find that the new, multidimensional GOLD A–D classification provides better diagnostic separation as it identifies more individuals at high risk of exacerbations than a classification entirely based on the level of FEV_1. Second, we also find that survival is better in the more severe COPD group C (low lung function but less dyspnea) than in the less severe group B (much better lung function but more dyspnea). We show that this is most likely caused by comorbidities, in particular heart disease.

Chronic obstructive pulmonary disease (COPD) has emerged as the most important respiratory disease globally, and its prevalence and impact on the society are expected to increase even further in the years to come. The *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease* document, produced by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), is one of the key inspirations for local COPD guidelines and thus the ideas expressed in such document are followed by thousands of practicing clinicians worldwide (1).

Stratification of patients according to severity of COPD is important to initiate relevant treatment and is one of the most crucial aspects of a management guideline. In the 2011 update of the GOLD document on COPD, a profound change in the stratification of the patients has been introduced (1). In the previous version, the classification of severity was mainly based on the FEV_1 level, whereas the new stratification also includes the level of daily symptoms, in particular dyspnea, and the history of exacerbations (Figure 1) (1, 2). In the present study, we wanted to compare the abilities of the old stratification (GOLD 2007) and the new stratification (GOLD 2011) regarding predicting exacerbations, hospital admissions, and mortality. We used the data from two large

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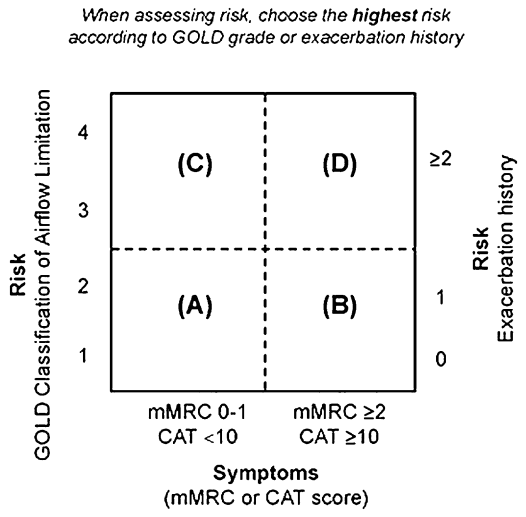

Figure 1. Combined assessment of chronic obstructive pulmonary disease (COPD) using Global Initiative for Obstructive Lung Disease (GOLD) based on FEV_1, modified Medical Research Council (mMRC), and exacerbation history. CAT = COPD Assessment Test. Reproduced by permission from Reference 1.

population-based studies in the area of Copenhagen, comprising in total more than 60,000 individuals and including more than 6,500 subjects with COPD. Some of the results have been previously reported in the form of an abstract (3).

METHODS

Participants

In the present study we pooled data from two similar but independent studies: the fourth examination of the Copenhagen City Heart Study (CCHS) in 2001–2003 and the examination of the Copenhagen General Population Study (CGPS) in 2003–2010. These studies were approved by institutional review boards and Danish ethics committees (KF100.2039/91, H-KF01-144/01), and were conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Copenhagen City Heart Study. The CCHS is a prospective epidemiologic study initiated in 1976–1978. A sample of 19,698 subjects aged 20 to 100 years was selected at random from the national Danish Civil Registration System, after age stratification in 5-year age groups, from residents of inner Copenhagen, and 14,223 subjects participated in the initial survey at Copenhagen University Hospital (4). They were all reinvited to participate in later surveys along with additional subjects in the youngest age groups. A total of 6,237 attended the fourth survey in 2001–2003 (response rate, 50%) (5).

Copenhagen General Population Study. The CGPS is a prospective epidemiologic study that aims to recruit more than 100,000 subjects representative of the general population and to collect genotypic and phenotypic data of relevance to a wide range of health-related problems. It is designed almost identically to the CCHS. Recruitment began in 2003 and is still ongoing (response rate, 45%) (6).

Initial Investigation and Stratification

In both studies, the participants filled in an extensive questionnaire concerning lifestyle and health topics, including medication use at home. A physical examination was performed, in which basic variables such as weight and height were measured. A spirometer (Vitalograph, Maids Moreton, Buckinghamshire, UK) was used in the CCHS and for the first 14,624 participants in the CGPS. An EasyOne diagnostic spirometer (ndd Medizintechnik, Zurich, Switzerland) was used with the remaining participants in the CGPS. Spirometry was performed in the standing position without the use of a nose clip. Three sets of FEV_1 and FVC values were obtained and as a criterion for correct performance of the procedure at least two measurements differing by less than 5% had to be produced together with the correct visual appearance of the spirometry tracings. The highest obtained values for every single participant of both FEV_1 and FVC were used. Only prebronchodilator measurements were available.

Individuals with COPD were identified according to international COPD guidelines, based on an FEV_1/FVC ratio less than 0.7. In accordance with the GOLD document we excluded individuals with self-reported asthma (1). In the present analyses, we included only individuals at least 40 years of age. Among 5,919 participants in the CCHS and 55,731 participants in the CGPS we identified 6,628 individuals fulfilling the above-mentioned COPD criteria. They were subdivided according to the two GOLD stratifications, using the FEV_1 level, expressed as a percentage of the predicted value (FEV_1%pred):

GOLD1: Mild COPD: $FEV_1\%pred \geqslant 80$

GOLD2: Moderate COPD: $80 > FEV_1\%pred \geqslant 50$

GOLD3: Severe COPD: $50 > FEV_1\%pred \geqslant 30$

GOLD4: Very severe COPD: $30 > FEV_1\%pred$

Covariates

The GOLD 2011 classification into groups A–D was, in addition to FEV_1%pred, also based on the self-reported severity of dyspnea (modified Medical Research Council [mMRC]) and on the frequency of COPD exacerbations in the last year. To define exacerbations, we used information regarding hospital admissions because of COPD and the use of oral corticosteroids and antibiotics related to treatment of exacerbations. For each individual, we defined an observation window of 1 year before the examination date and analyzed the use of inhaled medications and contacts with the region's hospitals during this period. This was done using the unique personal civil registration number assigned to all Danish inhabitants and by linking our database to two national registries: the Danish National Patient Registry, covering all hospital contacts in Denmark, and the Danish Registry of Medicinal Product Statistics, which contains information on all prescriptions dispensed in all Danish pharmacies (7, 8). We identified the relevant medications using the Anatomic Therapeutic Chemical (ATC) code (9). From the Danish National Patient Registry, we identified hospital admissions with a discharge diagnosis of COPD (International Classification of Diseases 10th edition: DJ41–44). An exacerbation of COPD was defined as a short course of treatment with prednisolone (up to 3 wk) alone or in combination with an antibiotic or an acute admission to hospital because of COPD. There were only a few subjects (n = 4) who received continuous treatment with oral prednisolone for COPD, and in these subjects exacerbations were defined by usage of antibiotics only, as it was difficult to estimate short-term changes in their use of oral corticosteroids. No individuals received continuous antibiotic treatment for COPD.

We also performed analyses of the subgroups of the GOLD C and D categories, as patients can be stratified into these categories through different scenarios:

- $FEV_1 < 50\%$pred *and* fewer than two exacerbations in the previous year (scenario 1: C_1 or D_1)
- $FEV_1 \geqslant 50\%$pred *and* two or more exacerbations in the previous year (scenario 2: C_2 or D_2)
- $FEV_1 < 50\%$pred *and* two or more exacerbations in the previous year (scenario 3: C_3 or D_3)

Thus, we subdivided categories C and D into subgroups C_1, C_2, C_3, D_1, D_2, and D_3, defined above, depending on which scenario was causing the individuals to be in category C or D.

The presence of ischemic heart disease and previous myocardial infarction was determined by means of a questionnaire and by using information from the Danish National Patient Registry.

End Points

After the examination date, the participants were monitored by means of the registries up to 8.9 years, with an average of 4.3 years.

The following end points were defined:

- COPD exacerbation (defined on the basis of the medication used and hospital admissions)
- Admissions to hospital (due both to COPD and with other diagnoses)
- All-causes mortality until August 17, 2010

Cause-specific mortality was determined according to the 10th classification of the International Classification of Diseases (ICD): respiratory deaths (J00–99), cardiovascular deaths (I00–99), cancer deaths (C00–D09) until December 31, 2009.

We also report the future prevalence of treatment with inhaled medications.

Statistics

All analyses were performed with R version 2.13.1 (R Foundation for Statistical Computing, Vienna, Austria). For demographics, analysis of variance was used for continuous variables and chi-square tests were used for categorical variables. To account for censoring of data, the Kaplan-Meier estimator was used to estimate the percentage of events during follow-up. Hence, in Tables 3 and 5 all percentages are 100% minus the Kaplan-Meier estimate of being event-free. The log-rank test was used to compare the difference in exacerbations, hospital admissions, and mortality within GOLD subgroups 1–4 and A–D. Last, we tested the predictive accuracy of GOLD 2011 A–D stratification compared with GOLD 2007 1–4 stratification regarding the prediction of exacerbations. We decided to test the following strata: A + B versus C + D against 1 + 2 versus 3 + 4 for exacerbations during the first year of follow-up. We report Harrell's *C*-statistic, which assesses the prognostic ability of a variable using a binary outcome (at least one exacerbation vs. no exacerbations). The data set was split in half: one-half for developing the models and the other half for validating the models.

RESULTS

A total of 6,628 individuals fulfilled our COPD inclusion criteria based on spirometry, age, and absence of asthma. Table 1 shows the shift from the 2007 1–4 GOLD classification to the 2011 A–D classification. The new classification results in more individuals belonging to the most severe group, group D, in the 2011 update (n = 292) in comparison with only 45 individuals belonging to the most severe group, group 4, in the 2007 classification.

The general characteristics of the individuals with COPD according to the two classifications are shown in Table 2. The patients with more severe dyspnea (groups B and D) are older than those with less dyspnea (groups A and C) ($P < 0.001$). The percentage of individuals with exacerbations during the year before the examination is relatively low, reflecting that this is a cohort recruited from the general population and not in a hospital setting. In general, the prevalence of individuals receiving inhaled medications is low, and almost 50% of individuals in the most severe categories are not treated at all. The prevalence of ischemic heart disease and previous myocardial infarction is significantly higher in subgroups B and D than in subgroups A and C.

Prognosis

Table 3 shows the 1- and 3-year prognosis according to the two GOLD stratifications. In general, the old classification 1–4 reflected prognosis well, with increasing prevalence of all investigated end points with increasing GOLD group. The new A–D classifications was a good predictor regarding exacerbations, with groups C and D experiencing a much higher incidence in the following years and a higher average number of exacerbations per year than groups A and B ($P < 0.001$). Harrell's *C*-statistic for GOLD 2011 regarding predicting exacerbations during the first year of observation was 0.70 (95% confidence interval [CI], 0.66–0.74), which was significantly higher than the 0.59 (95% CI, 0.55–0.62) based on GOLD 2007 ($P < 0.001$). This indicates a better predictive performance of the 2011 revision regarding predicting future exacerbations.

However, regarding mortality, the trend was not the same, as group B had higher mortality than group C (log-rank test, $P = 0.02$), which is also shown in Figure 2 depicting survival according to both GOLD 1–4 and GOLD A–D. The difference in survival between groups B and C remained statistically significant after inclusion of age and sex in the model (Cox proportional hazards; $P = 0.03$). In particular, the mortality from cardiovascular diseases and cancer was significantly higher in group B compared with group A (log-rank test, $P < 0.001$ for both) and in group D compared with group C (log-rank test, $P = 0.008$ for cardiovascular deaths and $P = 0.01$ for cancer deaths). A similar trend was seen regarding hospital admissions due to all causes, where group B experienced a higher risk of admission than group C (log-rank test, $P < 0.001$).

The probability of being treated with inhaled medication increased significantly after participation in our survey, especially in the most severe groups: after 3 years almost 82% in group 4 and 74% in group D were receiving inhaled medications for COPD (Table 3).

Subgroups of the C and D Categories

The distribution of the 271 individuals belonging to group C and of the 292 individuals belonging to group D according to the C_1–D_3 subgroups and their characteristics are shown in Table 4. The major criterion of placing the individuals in groups C and D was the low level of FEV_1 (77%), but there were 95 individuals (17%) (C_2 + D_2: 62 + 33) stratified to group C or D because of frequent exacerbations only. The number of individuals with both low FEV_1 and frequent exacerbations was only 34 (6%) and especially subgroup C_3 (mMRC < 2 *and* FEV_1 < 50%pred *and* two or more exacerbations in the previous year) was very small, comprising only six individuals. Groups C_2 and D_2 ($FEV_1 \geq 50$%pred *and* two or more exacerbations in the previous year) differed from the other subgroups by comprising

TABLE 1. CHANGE FROM GOLD 2007 TO GOLD 2011 CLASSIFICATION OF 6,628 INDIVIDUALS WITH SPIROMETRICALLY DEFINED CHRONIC OBSTRUCTIVE PULMONARY DISEASE: CONTINGENCY TABLE

GOLD 2007/GOLD 2011	GOLD A	GOLD B	GOLD C	GOLD D
GOLD 1, n = 3,306	2,961 (89.6%)	299 (9.0%)	37 (1.1%)	9 (0.3%)
GOLD 2, n = 2,851	2,165 (75.9%)	637 (22.3%)	25 (0.9%)	24 (0.8%)
GOLD 3, n = 426	—	—	201 (47.2%)	225 (52.8%)
GOLD 4, n = 45	—	—	8 (17.8%)	37 (82.2%)

Definition of abbreviation: GOLD = Global Initiative for Obstructive Lung Disease.
Each percent value shows the row percent.

TABLE 2. DISTRIBUTION OF 6,628 INDIVIDUALS WITH COPD AT BASELINE ACCORDING TO GOLD 2007 AND GOLD 2011 CLASSIFICATION

	GOLD 2007					GOLD 2011				
	1 (*n = 3,306*)	2 (*n = 2,851*)	3 (*n = 426*)	4 (*n = 45*)	*P* Value	A (*n = 5,126*)	B (*n = 936*)	C (*n = 271*)	D (*n = 292*)	*P* Value
Males, %	46	48	52	60	0.012	48	44	49	50	0.152
Age, yr (SD)	66 (12)	66 (11)	70 (9)	68 (9)	<0.001	65 (11)	71 (11)	69 (10)	72 (9)	<0.001
BMI, kg/m^2 (SD)	25.2 (3.9)	25.8 (4.4)	25.5 (4.9)	25.7 (4.6)	<0.001	25.2 (3.9)	27.3 (4.8)	24.9 (3.9)	26.1 (5.2)	<0.001
FEV_1, %pred (SD)	94.7 (11.3)	67.8 (8.1)	42.6 (5.1)	24.6 (4.6)	NA	83.8 (16.3)	74.2 (16.3)	51.8 (19.5)	43.3 (14.7)	NA
mMRC ⩾ 2, %	9.3	23.2	52.8	82.2	<0.001	0	100	0	100	NA
Never-smokers, %	26.0	13.6	7.0	4.7	<0.001	21.2	14.9	11.3	6.3	<0.001
Current smokers, %	32.5	47.9	50.4	39.5	<0.001	39.5	41.2	55.1	38.8	<0.001
Sedentary, %	6.5	11.9	18.9	22.2	<0.001	6.9	20.9	9.0	24.6	<0.001
No exacerbations in previous year, %	97.5	96.6	87.8	80	<0.001	98.7	97.8	72.0	72.9	<0.001
Two or more exacerbations in previous year, %	1.4	1.7	6.8	11.1	<0.001	0	0	25.1	20.7	NA
Any inhaled medication, %	4.2	12.1	36.6	55.6	<0.001	5.4	19.6	18.8	52.5	<0.001
On LABA, LAMA, or ICS, %	2.9	8.3	30.0	51.1	<0.001	3.6	13.7	15.5	43.4	<0.001
Ischemic heart disease, %	7.8	10.8	15.5	13.3	<0.001	7.0	20.7	10.3	19.3	<0.001
Myocardial infarction, %	3.1	5.3	8.7	8.9	<0.001	3.3	8.2	6.3	10.2	<0.001

Definition of abbreviations: BMI = body mass index; GOLD = Global Initiative for Obstructive Lung Disease; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; mMRC = modified Medical Research Council scale; NA = not applicable.

a high prevalence of women with much higher prevalence of never-smokers, suggesting a specific phenotype.

The prognosis for the C_1–D_3 subgroups is given in Table 5 and showed considerable heterogeneity regarding future exacerbation: subgroups C_1 and D_1 ($FEV_1 < 50\%$pred *and* fewer than two exacerbations in the previous year) had a much lower risk of exacerbations than the other groups (log-rank test, $P < 0.001$). Regarding mortality, the overall trend was that low lung function and the presence of dyspnea were a stronger predictor of death than exacerbation history, although we did observe high mortality in subgroup C_2 (mMRC < 2 *and* $FEV_1 \geqslant 50\%$pred *and* two or more exacerbations in the previous year).

DISCUSSION

This is to our knowledge the first study focusing on the distribution and prognosis of individuals in the general population according to the novel GOLD 2011 classification. Compared with the older

TABLE 3. ONE- AND THREE-YEAR PROGNOSIS FOR PARTICIPANTS ACCORDING TO GOLD 2007 AND GOLD 2011 CLASSIFICATIONS

	GOLD 2007					GOLD 2011				
	1 (*n = 3,306*)	2 (*n = 2,851*)	3 (*n = 426*)	4 (*n = 45*)	*P* Value*	A (*n = 5,126*)	B (*n = 936*)	C (*n = 271*)	D (*n = 292*)	*P* Value*
One-year prognosis										
Exacerbations, n (%)	88 (2.7)	145 (5.1)	66 (15.5)	17 (37.8)	<0.001	111 (2.2)	54 (5.8)	68 (25.1)	83 (28.3)	<0.001
Average number of exacerbations per year	0.1	0.1	0.4	1.1	<0.001	0·0	0.1	0.7	0.8	<0.001
Hospital admission due to COPD, n (%)	6 (0.2)	38 (1.3)	33 (7.8)	11 (24.4)	<0.001	13 (0.3)	28 (3.0)	7 (2.6)	40 (13.6)	<0.001
Hospital admission due to all causes, n (%)	720 (21.8)	763 (26.8)	144 (33.8)	17 (37.8)	<0.001	1,088 (21.2)	354 (37.8)	69 (25.5)	133 (45.1)	<0.001
Death, n (%)	23 (0.7)	28 (1.0)	10 (2.3)	1 (2.2)	0.007	31 (0.6)	19(2.0)	2 (0.7)	10 (3.4)	<0.001
Future treatment with inhaled medication, n (%)	181 (5.5)	525 (18.5)	214 (50.3)	33 (73.3)	<0.001	434 (8.5)	249 (26.7)	87 (32.1)	183 (62.1)	<0.001
Three-year prognosis										
Exacerbations, n (%)	186 (6.1)	329 (12.4)	138 (34.4)	26 (66.0)	<0.001	297 (6.4)	141 (17.0)	94 (35.9)	147 (53.1)	<0.001
Average number of exacerbations per year	0.1	0.1	0.5	1.4	<0.001	0.0	0.2	0.6	0.9	<0.001
Hospital admission due to COPD, n (%)	27 (0.9)	120 (4.7)	83 (20.9)	18 (42.5)	<0.001	63 (1.4)	73 (8.9)	21 (8.5)	91 (33.3)	<0.001
Hospital admission due to all causes, n (%)	1,489 (48.0)	1,524 (55.5)	258 (62.2)	29 (67.3)	<0.001	2,336 (48.2)	612 (67.8)	139 (53.1)	213 (74.4)	<0.001
Death, n (%)	118 (4.0)	154 (5.9)	57 (14.3)	11 (25.8)	<0.001	173 (3.8)	91 (10.6)	20 (8.2)	56 (20.1)	<0.001
Cardiovascular death,† n (%)	16 (0.6)	34 (1.4)	8 (2.2)	2 (4.5)	<0.001	27 (0.6)	22 (2.9)	1 (0.5)	10 (4.0)	<0.001
Respiratory death,† n (%)	2 (0.1)	2 (0.1)	8 (2.3)	3 (10.1)	<0.001	2 (0.1)	2 (0.3)	1 (0.4)	10 (4.4)	<0.001
Cancer death,† n (%)	16 (0.6)	27 (1.1)	8 (2.1)	0 (0.0)	0.01	25 (0.6)	16 (2.1)	1 (0.4)	9 (3.5)	<0.001
Future treatment with inhaled medication, n (%)	299 (10.2)	788 (29.5)	269 (64.9)	36 (81.8)	<0.001	709 (15.3)	346 (40.1)	123 (48.1)	214 (74.1)	<0.001

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Obstructive Lung Disease.

All percentages are Kaplan-Meier estimates.

* *P* values are based on log-rank test for time to event data and on negative binomial regression for annual rates.

† Indicates that the number of deaths with known death causes is smaller than the total number of deaths due to shorter observation period for the cause-specific mortality.

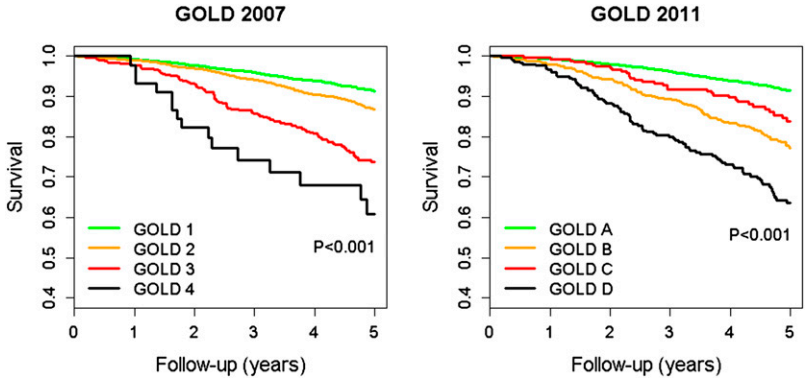

Figure 2. Survival shown as Kaplan-Meier curves according to the GOLD 2007 classification (*left*) and GOLD 2011 classification (*right*).

version, which was based mainly on the level of FEV_1, the new multidimensional classification identifies a higher numbers of individuals at risk of exacerbations, thus providing a better prognostic separation as shown by the Harrell *C*-statistic.

The setting of our study in the general population is the most likely explanation for the observation that the majority of our individuals were treatment naive. In fact, only in group D were more than 50% of the participants receiving inhaled medication at the time of examination. This reflects clearly the underdiagnosis of COPD in the general population and is in line with studies focusing on the substantial need for an earlier diagnosis of COPD (10, 11). After participation in our survey, the individuals were informed of the results of their health examination and it is reassuring to observe that this resulted in more individuals starting relevant medical treatment (Table 3).

In our cohort, a history of repeated exacerbations (two or more in the previous year) was a good predictor of subsequent exacerbations. Thus, although the prevalence of "frequent exacerbators" was lower in our sample, we could reproduce the findings from the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study in our general population sample (12). In fact, our figures describing the risk of an exacerbation in the year to come (groups C_2 and C_3 and groups D_2 and D_3; the groups with two or more exacerbations in the previous year) (Table 5) are quite comparable to the findings in the ECLIPSE cohort: approximately 70% of those who had at least two exacerbations in the previous year experienced a new exacerbation in the following year. Similarly, less than 20% of those with $FEV_1 < 50\%$pred and less than two exacerbations in the previous year experienced an exacerbation next year.

The main role of the new A–D stratification is to suggest first-line medical treatment for the patients within these categories. The patients belonging to groups C and D have been defined as those with a higher risk of disease progression and the treatments suggested for these individuals include inhaled corticosteroids and possibly $Phosphodiesterase_4$ inhibitors (1). However, groups C and D consist of individuals with quite variable lung function and a variable history of exacerbations, which is mirrored by quite distinct prognosis regarding risk of exacerbations and mortality (Table 5). In the setting of the general population, which is more comparable to the situation in the office of a general practitioner than to a specialized COPD clinic, the majority of the patients in groups C and D are stratified into these groups because of low FEV_1 level (77%; Table 3) and are thus at low risk of exacerbation, although they

TABLE 4. DISTRIBUTION OF 576 INDIVIDUALS WITHIN GROUPS C AND D ACCORDING TO 2011 COPD CLASSIFICATION, BASED ON PERCENT PREDICTED FEV_1 AT BASELINE AND NUMBER OF EXACERBATIONS IN PREVIOUS YEAR

	C Subgroups of GOLD 2011				D Subgroups of GOLD 2011			
	C_1: FEV_1 < 50%pred and < 2 exa (*n* = 203)	C_2: FEV_1 ⩾ 50%pred and ⩾ 2 exa (*n* = 62)	C_3: FEV_1 < 50%pred and ⩾ 2 exa (*n* = 6)	C Subgroup *P* Value	D_1: FEV_1 < 50%pred and < 2 exa (*n* = 234)	D_2: FEV_1 ⩾ 50%pred and ⩾ 2 exa (*n* = 33)	D_3: FEV_1 < 50%pred and ⩾ 2 exa (*n* = 28)	D Subgroup *P* Value
Males, %	56	27	50	<0.001	51	42	50	0.644
Age, yr (SD)	68 (10)	73 (9)	73 (8)	<0.001	71 (9)	74 (11)	75 (7)	0.024
BMI, kg/m^2 (SD)	25.0 (4.1)	24.9 (3.3)	23.5 (2.7)	0.670	26.0 (5.4)	26.5 (4.6)	26.0 (4.2)	0.883
FEV_1, %pred (SD)	42.8 (6.1)	82.8 (16.7)	37.7 (7.3)	<0.001	39.7 (7.8)	73.1 (21.2)	38.4 (8.5)	<0.001
mMRC ⩾ 2, %	0.0	0.0	0.0	NA	100.0	100.0	100.0	NA
Never-smokers, %	8.6	21.0	0.0	0.034	5.3	12.9	7.1	0.204
Current smokers, %	61.4	37.1	33.3	0.002	43.6	25.8	14.3	0.002
Sedentary, %	9.5	6.6	16.7	0.477	27.3	6.7	21.4	0.031
No exacerbations in previous year, %	96.1	0.0	0.0	NA	91.9	0.0	0.0	NA
Two or more exacerbations in previous year, %	0.0	100.0	100.0	NA	0.0	100.0	100.0	NA
Any inhaled medication, %	18.7	16.1	50.0	0.146	49.6	45.5	85.7	0.001
On LABA, LAMA, or ICS, %	15.8	11.3	50.0	0.058	39.3	36.4	85.7	<0.001
Ischemic heart disease, %	9.9	12.9	0.0	0.734	18.8	15.2	28.6	0.349
Myocardial infarction, %	6.9	4.8	0.0	0.844	11.1	9.1	3.6	0.567

Definition of abbreviations: BMI = body mass index; exa = exacerbations; GOLD = Global Initiative for Obstructive Lung Disease; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; mMRC = modified Medical Research Council scale; NA = not applicable.

TABLE 5. ONE- AND THREE-YEAR PROGNOSIS FOR PATIENTS IN SUBGROUPS C AND D

	C Subgroups of GOLD 2011				D Subgroups of GOLD 2011			
	C_1: FEV_1 < 50%pred and < 2 exa (*n = 203*)	C_2: FEV_1 ⩾ 50%pred and ⩾ 2 exa (*n = 62*)	C_3: FEV_1 < 50%pred and ⩾ 2 exa (*n = 6*)	C Subgroup *P* Value*	D_1: FEV_1 < 50%pred and < 2 exa (*n = 234*)	D_2: FEV_1 ⩾ 50%pred and ⩾ 2 exa (*n = 33*)	D_3: FEV_1 < 50%pred and ⩾ 2 exa (*n = 28*)	D Subgroup *P* Value*
One-year prognosis								
Exacerbations, n (%)	16 (7.9)	47 (75.8)	5 (83.3)	<0.001	43 (18.5)	21 (63.6)	19 (68.8)	<0.001
Hospital admissions due to COPD, n (%)	6 (3.0)	1 (1.6)	0 (0.0)	0.78	28 (12.0)	2 (6.1)	10 (36.4)	<0.001
Hospital admissions all causes, n (%)	49 (24.1)	18 (29.0)	2 (33.3)	0.55	96 (41.0)	23 (69.7)	14 (50.0)	0.002
Death, n (%)	1 (0.5)	1 (1.6)	0 (0.0)	0.65	8 (3.4)	0 (0.0)	2 (7.1)	0.30
Future treatment with inhaled medications, n (%)	74 (36.5)	9 (14.5)	4 (66.7)	<0.001	146 (62.5)	14 (42.4)	23 (82.1)	0.002
Three-year prognosis								
Exacerbations, n (%)	38 (20.1)	51 (83.2)	5 (83.3)	<0.001	98 (45.4)	26 (79.8)	23 (87.5)	<0.001
Hospital admissions due to COPD, n (%)	17 (9.2)	3 (5.6)	1 (16.7)	0.48	67 (30.8)	8 (27.8)	16 (62.1)	<0.001
Hospital admissions all causes, n (%)	96 (48.6)	39 (66.7)	4 (66.7)	0.03	161 (71.0)	26 (81.3)	26 (92.9)	0.002
Death, n (%)	14 (7.6)	5 (8.8)	1 (20.0)	0.65	43 (19.4)	3 (10.3)	10 (36.6)	0.02
Future treatment with inhaled medications, n (%)	104 (53.6)	15 (27.5)	4 (66.7)	<0.001	172 (75.0)	17 (54.4)	25 (89.3)	<0.001

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; exa = exacerbations; GOLD = Global Initiative for Obstructive Lung Disease.
All percentages are Kaplan-Meier estimates.
* *P* values are based on log-rank test for time to event data and negative binomial regression for annual rates.

have more hospital admissions than individuals in groups A and B (Tables 3 and 5). Hence, although the new GOLD recommendations seem sound for groups C and D in general, our findings suggest that in the setting outside pulmonary clinics the vast majority of individuals in these groups are at low risk of COPD exacerbation in the future, and that this should be taken into account when choosing an appropriate treatment.

Our findings substantiate the importance of dyspnea as a predictor of poor survival (13–15). We believe that the presence of an underlying disease causing dyspnea is responsible for the quite surprising finding of the significantly poorer survival of group B compared with group C, despite a much lower FEV_1%pred in the latter group. This is in line with a high prevalence of both diagnosed and unrecognized heart disease but also of cancer (5, 16–19). Our findings underline the importance of searching for comorbidities in individuals with COPD, a notion that has come into increasing focus and is also acknowledged in the new GOLD revision (1, 20–22). These comorbidities are not only present in the most severe disease category (group D) but also in the less severe disease category (group B). Also importantly, the presence of these comorbidities, in particular heart disease, results in the fact that using the A–D categories as a definite and precise guide to COPD therapy can be problematic, as dyspnea in some patients with COPD may benefit more from treatment of heart disease than from an uncritical increase in inhaled medications. We therefore suggest that in the next revision of GOLD, comorbidities should be included in the staging of COPD.

A limitation of our study is the fact that it was not especially designed to detect COPD exacerbations. This means that mild exacerbations not treated with oral corticosteroids and antibiotics were overlooked. On the other hand, we used the generally accepted definition of an exacerbation, which is employed in most of the clinical trials of COPD and is in line with the GOLD document (1). Our findings are also affected by "nonresponder bias," and we are likely to underestimate of the prevalence of most severe COPD cases (23). Yet, as we are using prebronchodilator values to classify participants, we are at the same time likely to overestimate the prevalence of milder cases. On the basis of our previous studies of reversibility in a similar population, which were done in connection with a randomized trial, we do not think that lack of postbronchodilatory values for FEV_1 has a significant influence on our results and conclusions (24). Last, we must acknowledge that the GOLD system is designed for use in clinical practice, whereas we have tested it in an epidemiological setting.

In conclusion, our analysis of a large sample of individuals with COPD selected from the general population shows that the new multidimensional GOLD A–D classification provides better diagnostic separation regarding predicting exacerbations than the GOLD 2007 1–4 stratification. Our findings also substantiate the role of dyspnea as the strong predictor of poor survival in COPD even among individuals with relatively preserved FEV_1, and we suggest that such individuals should be examined for the presence of heart disease. Last, our study shows that GOLD groups C and D are heterogeneous, being composed of phenotypes with variable risk of future exacerbations, and we suggest that this should be taken into account when planning treatment for these individuals.

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: revised 2011. Available from: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2011_Jan21.pdf
2. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, Fukuchi Y, Jenkins C, Rodriguez-Roisin R, van Weel C, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007;176:532–555.
3. Lange P, Marott J, Dahl M, Ingebrigtsen TS, Vestbo J, Nordestgaard B. Predicting the natural course of COPD using the old and the new GOLD classification. *Eur Respir J* 2012 Suppl 56:278s.
4. Appleyard M, Hansen AT, Schnohr P, Jensen G, Nyboe J. The Copenhagen City Heart Study: a book of tables with data from the

first examination (1976–78) and a five-year follow-up (1981–83). *Scand J Soc Med* 1989;170(Suppl 41):1–160.
5. Lange P, Mogelvang R, Marott JL, Vestbo J, Jensen JS. Cardiovascular morbidity in COPD: a study of the general population. *COPD* 2010;7: 5–10.
6. Stender S, Frikke-Smidth R, Nordestgaard BG, Tybjærg-Hansen A. Sterol transporter adenosine triphosphate–binding cassette transporter G8, gallstones, and biliary cancer in 62,000 individuals from the general population. *Hepatology* 2011;53:640–648.
7. Danish National Patient Registry. Available from: http://www.sst.dk/Indberetning%20og%20statistik/Landspatientregisteret
8. Gaist D, Sørensen HT, Hallas J. The Danish prescription registries. *Dan Med Bull* 1997;44:445–448.
9. WHO Collaborating Centre for Drug Statistics Methodology. Norwegian Institute of Public Health, ATC/DDD Index 2010. Available from: http://www.whocc.no/atc_ddd_index/
10. Lange P, Marott JL, Dahl M, Ingebrigtsen TS, Vestbo J, Nordestgaard BG. Substantial need for early diagnosis, rehabilitation and treatment of COPD. *Dan Med J* 2012;59:A4396.
11. Ulrik CS, Løkke A, Dahl R, Dollerup J, Hansen G, Cording PH, Andersen KK; TOP Study Group. Early diagnosis of COPD in general practice. *Int J Chron Obstruct Pulmon Dis* 2011;6:123–127.
12. Hurst J, Vestbo J, Anzueto A, Locantore N, Mülerova H, Tal-Singer R, Miller B, Lomas D, Agusti A, MacNee W, *et al.* Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010; 363:1128–1138.
13. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, Pinto Plata V, Cabral HJ. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:1005–1012.
14. Vestbo J, Knudsen KM, Rasmussen FV. Should we continue using questionnaires on breathlessness in epidemiologic surveys? *Am Rev Respir Dis* 1988;137:1114–1118.
15. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-yr survival than airway obstruction in patients with COPD. *Chest* 2002;121:1434–1440.
16. Rutten FH, Cramer MJ, Grobbee DE, Sachs AP, Kirkels JH, Lammers JW, Hoes AW. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. *Eur Heart J* 2005;26: 1887–1894.
17. Brekke PH, Omland T, Smith P, Soyseth V. Underdiagnosis of myocardial infarction in COPD—Cardiac Infarction Injury Score (CIIS) in patients hospitalised for COPD exacerbation. *Respir Med* 2008; 102:1243–1247.
18. McAllister DA, Maclay JD, Mills NL, Leitch A, Reid P, Carruthers R, O'Connor J, McAlpine L, Chalmers G, Newby DE, *et al*. Diagnosis of myocardial infarction following hospitalisation for exacerbation of COPD. *Eur Respir J* 2012;39:1097–1103.
19. Sode BF, Dahl M, Nordestgaard BG. Myocardial infarction and other co-morbidities in patients with chronic obstructive pulmonary disease: a Danish nationwide study of 7.4 million individuals. *Eur Heart J* 2011;32:2365–2375.
20. Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: role of comorbidities. *Eur Respir J* 2006;28:1245–1257.
21. Fabbri LM, Luppi F, Beghe B, Rabe KF. Complex chronic comorbidities of COPD. *Eur Respir J* 2008;31:204–212.
22. Mannino DM, Doherty DE, Buist SA. Global Initiative on Obstructive Lung Disease (GOLD) classification of lung disease and mortality: findings from the Atherosclerosis Risk in Communities (ARIC) Study. *Respir Med* 2006;100:115–122.
23. Jensen G. Epidemiology of chest pain and angina pectoris. *Acta Med Scand* 1983;214(Suppl 682):1–120.
24. Vestbo J, Sørensen T, Lange P, Torre P, Viskum K. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 1999;353:1819–1823.