Clinical and prognostic heterogeneity of C and D GOLD groups

To the Editor:

"High risk" groups for exacerbations of chronic obstructive pulmonary disease (COPD) in the 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD) proposal (*i.e.* groups C and D) [1] include: patients with a forced expiratory volume in 1 s FEV_1 <50% reference and <2 exacerbations $year^{-1}$ (subgroups C1 and D1); patients with ⩾2 exacerbations·$year^{-1}$ and an FEV_1 ⩾50% reference (subgroups C2 and D2); and patients with both FEV_1 <50% ref. and ⩾2 exacerbations·$year^{-1}$ (subgroups C3 and D3) [2–5]. We hypothesised that these high-risk subgroups will differ in other clinical, functional and biological characteristics and will be associated with different long-term outcomes. We explored this hypothesis in the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) cohort [6, 7].

The design and methodology of the ECLIPSE study (www.clinicaltrials.gov with identifier number NCT00292552; GSK study code SCO104960) has been published elsewhere in detail [6]. The study was approved by the Ethics Committees from the participating centres and all participants signed their informed consent [7]. Out of the 2164 GOLD grades II-IV patients included in the ECLIPSE study, 2101 (97%) had complete GOLD 2011 data [4] and were included in the current analysis; 1313 of them (62.5%) were classified as groups C (n=483, 36.8%) or D (n=830, 63.2%), using the modified Medical Research Council dyspnoea score to determine high and low COPD symptoms.

These analyses are exploratory and may have low power, since they are based on a subset of the COPD subjects enrolled in ECLIPSE. Results are shown as mean±SD or n (%), as appropriate. Kruskal–Wallis tests and Cochran–Mantel–Haenszel tests were used to assess differences in subject characteristics among groups. Kaplan–Meier curves were constructed to describe the occurrence of the first event for the following outcomes: moderate-to-severe exacerbations of COPD, hospitalisations for COPD exacerbation, and all-cause mortality over the study period. A p-value <0.05 (two sided) was considered statistically significant. No adjustments were made for multiple comparisons. SAS (version 9; SAS Institute, Inc., Cary, NC, USA) was used to conduct all analyses and figures were created *via* S-PLUS (TIBCO Software, Boston, MA, USA).

On the one hand, from the 483 group C patients, 336 (70%) 62 (13%) and 85 (18%) were classified in the subgroups C1, C2 and C3, respectively [4]. As expected, lung function was worse in subgroups C1 and C3 (both groups had clinically comparable airflow limitation), and exacerbations prior to the start of the study were more frequent in subgroups C2 and C3 (both groups had a comparable level of exacerbation history). The remaining variables were similar across groups (table 1). However, of note is that the C2 subgroup included more females and had less emphysema than the other two C subgroups.

On the other hand, from the 830 group D patients, 522 (63%), 72 (9%) and 236 (28%) were classified in subgroups D1, D2 and D3, respectively [4] (table 1). Similarly to group C patients, lung function was worse in subgroup D1 and D3 (both groups had clinically comparable airflow limitation), and previous exacerbations were more frequent in subgroups D2 and D3 (both groups had a comparable level of exacerbation history). Other variables were similar across groups, albeit the percentage of females and body mass index (BMI) was higher, and the extent of emphysema was lower, in the D2 subgroup (table 1). Of note, the 6-min walking distance (6MWD) was not different in subgroup D1 *versus* subgroup D2 but, at variance with the C subgroups, it was worse in subgroup D3.

Given that in 2013, GOLD included a new high-risk criteria (>1 hospitalisation due to COPD in the previous year) [1], we explored how this new criteria influenced the results discussed above. It caused 53 patients (2.5%) to change from a low- to high-risk group, 26 from group A to group C, and 27 from group B to group D.

Rate of moderate-to-severe exacerbation during follow-up was higher in those patients with a history of previous exacerbations (subgroups C2/C3 and D2/D3) (table 1 and fig. 1). Time to first hospitalisation was significantly worse in subgroups C3 and D3 but similar between subgroups C1/C2 and D1/D2 (fig. 1). All-cause mortality during follow-up was different in C subgroups (highest in C3 (14%), intermediate in C1 (9%) and absent (0%) in C2) but similar in D subgroups (D1 14%, D2 11% and D3 14%) (fig. 1). Finally, the rate of FEV_1 decline and the incidence of cardiovascular events or cancer during follow-up were not different across C and D subgroups (table 1). Both in GOLD groups C and D, age, FEV_1 %

TABLE 1 The main characteristics and outcomes for the three high-risk C and D subgroups

	C1	C2	C3	p-value			D1	D2	D3	p-value		
				C1 *versus* C2	C1 *versus* C3	C2 *versus* C3				D1 *versus* D2	D1 *versus* D3	D2 *versus* D3
Patients	336 (70%)	62 (13%)	85 (18%)				522 (63%)	72 (9%)	236 (28%)			
Demographics												
Age years	63.2±7.2	61.8 ±7.7	62.3 ±6.9	0.228	0.215	0.866	63.7±7.0	63.5±7.1	63.5±6.6	0.963	0.577	0.72
Female	95 (28%)	27 (44%)	27 (32%)	0.017	0.527	0.145	147 (28%)	41 (57%)	92 (39%)	<0.001	0.003	0.007
BMI kg·m^{-2}	25.1±5.0	25.9±4.7	25.2±5.0	0.299	0.961	0.444	26.3±6.0	29.0±7.3	26.3±5.7	0.003	0.826	0.007
FFMI kg·m^{-2}	16.7±2.5	17.1±2.6	16.6±2.4	0.365	0.895	0.416	17.0±2.8	17.9±3.3	17.0±2.9	0.027	0.74	0.028
Smoking pack-years	45.3±22.7	46.1±24.1	44.2±24.6	0.948	0.439	0.552	51.5±26.7	50.3±33.8	50.6±27.9	0.201	0.696	0.356
Period smoking years	39.7±10.4	39.9±10.0	39.4±7.7	0.769	0.413	0.347	40.2±9.6	40.8±8.3	40.8±10.0	0.878	0.305	0.65
Current smoker	143 (43%)	32 (52%)	32 (38%)	0.188	0.412	0.093	167 (32%)	26 (36%)	74 (31%)	0.485	0.862	0.451
Symptoms												
mMRC dyspnoea score	0.8±0.4	0.8±0.4	0.8±0.4	0.911	0.46	0.519	2.5±0.7	2.5±0.7	2.7±0.8	0.932	0.026	0.245
SGRQ-C total score	43.2±17.0	41.8±14.9	51.9±15.2	0.597	<0.001	<0.001	60.2±15.8	65.3±15.3	65.5±14.4	0.009	<0.001	0.933
Moderate-to-severe ECOPD[#]	0.3±0.5	2.5±1.0	2.8±1.5	<0.001	<0.001	0.133	0.4±0.5	2.8±1.1	2.9±1.2	<0.001	<0.001	0.423
CESD total score	9.2±8.2	10.1±7.4	10.0±8.9	0.166	0.558	0.552	12.5±9.2	15.3±10.5	15.3±10.0	0.033	<0.001	0.863
Chronic bronchitis	126 (38%)	28 (45%)	28 (33%)	0.256	0.436	0.133	195 (37%)	28 (39%)	95 (40%)	0.801	0.447	0.836
Physiology[¶]												
FEV_1[+] % pred	39.7±7.6	63.7±8.7	36.3±8.5	<0.001	<0.001	<0.001	35.1±8.7	60.2±9.3	35.1±8.5	<0.001	0.969	<0.001
FEV_1 % reversibility	10.1±13.5	8.7±9.7	12.1±15.7	0.517	0.491	0.259	10.3±14.7	9.6±10.9	10.4±15.2	0.835	0.97	0.852
FVC[+] % pred	81.4±17.4	99.5±16.5	81.3±18.9	<0.001	0.938	<0.001	74.8±17.0	96.0±15.5	78.1±19.1	<0.001	0.025	<0.001
RV % pred	175.1±48.8	147.0±36.1	184.1±50.5	0.038	0.271	0.023	180.9±47.4	122.6±29.3	189.7±56.3	<0.001	0.589	<0.001
TLC % pred	121.4±16.5	118.2±14.7	122.8±18.9	0.612	0.532	0.351	121.1±18.4	110.2±15.3	123.8±19.4	0.025	0.726	0.014
FRC % pred	157.0±29.3	137.8±27.3	162.2±34.1	0.017	0.381	0.011	160.9±35.1	124.2±26.0	161.7±36.7	<0.001	0.935	<0.001
S_{aO_2} %	94.4±3.0	95.6±2.2	93.7±4.4	<0.001	0.188	<0.001	93.6±3.2	95.1±2.0	93.7±3.3	<0.001	0.5	<0.001
6MWD m	405±108	446±97	394±97	0.016	0.515	0.011	313±117	320±92	289±111	0.633	0.007	0.033
BODE index	2.8±1.0	0.8±0.8	3.0±1.0	<0.001	0.192	<0.001	5.1±1.5	3.3±1.2	5.5±1.6	<0.001	0.014	<0.001
Imaging												
% LAA –950 HU	19.9±11.1	10.7±8.2	21.3±13.0	<0.001	0.429	<0.001	22.9±13.2	15.2±9.8	24.0±11.9	<0.001	0.178	<0.001
Systemic inflammation												
WBC $10^9 \cdot L^{-1}$	7.6 (2.5)	7.6 (2.3)	7.4 (2.6)	0.584	0.312	0.749	7.8 (2.6)	7.7 (2.7)	8.0 (2.6)	0.779	0.106	0.264
Neutrophils $10^9 \cdot L^{-1}$	4.9 (2.3)	4.4 (1.8)	4.9 (2.1)	0.105	0.467	0.376	5.2 (2.2)	4.8 (2.5)	5.2 (2.4)	0.263	0.198	0.075
Neutrophils %	65.5 (11.2)	62.1 (11.4)	66.3 (11.2)	<0.001	0.922	0.006	66.9 (11.3)	65.1 (12.7)	67.0 (10.5)	0.05	0.865	0.047
Eosinophils $10^9 \cdot L^{-1}$	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)	0.481	0.253	0.164	0.2 (0.2)	0.2 (0.1)	0.2 (0.2)	0.994	0.056	0.217
Eosinophils %	2.6 (2.3)	3.1 (2.7)	2.3 (2.9)	0.342	0.446	0.256	2.3 (1.9)	2.1 (1.4)	2.4 (2.6)	0.943	0.187	0.486
hsCRP mg·L^{-1}	2.5 (4.2)	2.7 (5.7)	4.0 (5.9)	0.478	0.024	0.031	3.7 (7.5)	3.9 (6.3)	4.5 (7.8)	0.615	0.028	0.381
IL-6 pg·mL^{-1}	1.4 (2.1)	1.2 (1.7)	1.4 (2.1)	0.096	0.993	0.184	1.8 (2.7)	2.1 (2.4)	1.8 (2.9)	0.545	0.67	0.507
IL-8 pg·mL^{-1}	6.4 (9.5)	6.6 (9.3)	6.7 (8.6)	0.641	0.812	0.888	7.0 (10.6)	8.8 (10.4)	7.5 (9.1)	0.315	0.381	0.54
Fibrinogen mg·dL^{-1}	442.0 (125.0)	436.5 (152.5)	466.0 (132.0)	0.528	0.04	0.071	470.0 (147.5)	457.3 (106.0)	483.0 (134.0)	0.522	0.029	0.032
TNF-α ng·mL^{-1}	2.4 (0.0)	2.4 (51.4)	2.4 (4.8)	0.001	0.486	0.036	2.4 (2.7)	2.4 (7.4)	2.4 (0.0)	0.681	0.335	0.313
CC-16 ng·mL^{-1}	5.1 (3.0)	4.6 (3.5)	5.4 (4.2)	0.116	0.788	0.154	4.8 (3.4)	4.7 (3.4)	4.9 (3.4)	0.168	0.906	0.191
CCL-18 ng·mL^{-1}	100.0 (48.8)	103.1 (48.2)	98.9 (49.6)	0.24	0.318	0.702	107.1 (59.0)	109.9 (56.9)	114.0 (54.7)	0.408	0.112	0.838
SPD ng·mL^{-1}	118.4 (91.2)	120.4 (58.9)	133.1 (95.0)	0.663	0.108	0.113	121.3 (85.0)	122.8 (99.2)	115.8 (87.0)	0.763	0.167	0.665

Continued

TABLE 1 Continued

	C1	C2	C3	p-value			D1	D2	D3	p-value		
				C1 *versus* C2	C1 *versus* C3	C2 *versus* C3				D1 *versus* D2	D1 *versus* D3	D2 *versus* D3
Concomitant medications												
Medications containing ICS	241 (72%)	44 (71%)	79 (93%)	0.903	<0.001	<0.001	421 (81%)	63 (88%)	218 (92%)	0.161	<0.001	0.201
Tiotropium	146 (43%)	23 (37%)	50 (59%)	0.353	0.011	0.01	271 (52%)	43 (60%)	135 (57%)	0.214	0.177	0.705
Statins	69 (21%)	12 (19%)	15 (18%)	0.832	0.552	0.792	126 (24%)	17 (24%)	44 (19%)	0.922	0.093	0.355
Comorbidities[§]												
Heart trouble	64 (19%)	10 (16%)	15 (18%)	0.561	0.839	0.735	151 (30%)	20 (28%)	63 (28%)	0.796	0.551	0.914
Hypertension	113 (35%)	17 (30%)	23 (29%)	0.477	0.316	0.892	203 (41%)	28 (42%)	93 (41%)	0.797	0.922	0.854
Angina	25 (8%)	5 (8%)	8 (10%)	0.936	0.536	0.71	47 (10%)	11 (16%)	32 (14%)	0.099	0.09	0.637
Heart attack	16 (5%)	0	6 (7%)	0.076	0.381	0.03	46 (9%)	10 (15%)	24 (10%)	0.138	0.548	0.331
Stroke	9 (3%)	4 (7%)	3 (4%)	0.124	0.678	0.409	17 (3%)	5 (7%)	7 (3%)	0.107	0.843	0.117
Heart failure	13 (4%)	1 (2%)	5 (6%)	0.364	0.396	0.184	48 (10%)	5 (8%)	15 (7%)	0.609	0.217	0.812
Arrhythmia	33 (10%)	5 (8%)	10 (12%)	0.671	0.617	0.481	61 (12%)	12 (19%)	30 (14%)	0.163	0.701	0.298
Osteoporosis	38 (12%)	9 (16%)	13 (16%)	0.4	0.305	0.967	57 (12%)	12 (17%)	49 (23%)	0.18	<0.001	0.351
Osteoarthritis	29 (9%)	12 (22%)	13 (17%)	0.005	0.049	0.456	53 (11%)	25 (36%)	34 (16%)	<0.001	0.056	<0.001
Rheumatoid arthritis	11 (3%)	2 (4%)	4 (5%)	0.902	0.498	0.729	12 (2%)	3 (5%)	7 (3%)	0.304	0.588	0.563
Inflammatory bowel disorder	10 (3%)	2 (3%)	5 (6%)	0.878	0.185	0.47	24 (5%)	8 (12%)	10 (4%)	0.019	0.868	0.031
Diabetes	22 (7%)	0	5 (6%)	0.042	0.847	0.056	60 (12%)	11 (15%)	21 (9%)	0.356	0.287	0.123
Peptic ulcer	36 (11%)	9 (16%)	5 (6%)	0.285	0.191	0.061	47 (9%)	8 (11%)	28 (12%)	0.587	0.21	0.821
Reflux/heartburn	65 (20%)	19 (32%)	17 (20%)	0.032	0.912	0.106	114 (23%)	34 (49%)	67 (30%)	<0.001	0.036	0.003
Depression requiring treatment	46 (14%)	9 (15%)	13 (15%)	0.814	0.734	0.961	84 (16%)	19 (27%)	51 (22%)	0.033	0.051	0.457
Anxiety/panic attacks	37 (11%)	8 (14%)	11 (13%)	0.566	0.598	0.927	97 (19%)	23 (32%)	58 (26%)	0.01	0.049	0.267
3-year follow-up												
Mortality rate	29 (9%)	0	12 (14%)	0.016	0.128	0.002	72 (14%)	8 (11%)	34 (14%)	0.532	0.822	0.476
Moderate-to-severe ECOPD rate per person-year	1.1 (1.2%)	1.6 (1.2%)	2.1 (1.8%)	<0.001	<0.001	0.451	1.2 (1.4%)	2.1 (1.7%)	2.6 (1.8%)	<0.001	<0.001	0.018
Rate of FEV_1 decline mL·year^{-1}	−28.0±47.6	−38.1±44.3	−33.5±36.8	0.15	0.426	0.559	−32.8±34.5	−31.0±42.6	−30.1±32.2	0.363	0.861	0.426
CV events	20 (6%)	4 (6%)	6 (7%)	0.88	0.705	0.886	29 (6%)	2 (3%)	19 (8%)	0.321	0.192	0.121
Lung cancer	3 (<1%)	1 (2%)	0	0.602	0.383	0.242	3 (<1%)	1 (1%)	1 (<1%)	0.429	0.791	0.373

Data are presented as n (%), mean±SD and median (interquartile range), unless otherwise stated. C1/D1: patients with forced expiratory volume in 1 s (FEV_1) <50% reference, <2 exacerbations·year^{-1} and low (C1) or high (D1) symptoms; C2/D2 patients with FEV_1 ⩾50% ref., ⩾2 exacerbations·year^{-1} and low (C2) or high (D2) symptoms; C3/D3: patients with both FEV_1 <50% ref., ⩾2 exacerbations·year^{-1} and low (C3) or high (D3) symptoms. Lung volumes were only assessed in a subset of the ECLIPSE cohort at select sites, therefore, ~30% of group C patients and 21% of group D patients had lung volume data. BMI: body mass index; FFMI: fat-free mass index; mMRC: modified Medical Research Council; SGRQ-C: St George's Respiratory Questionnaire for chronic obstructive pulmonary disease patients (COPD); ECOPD: exacerbation of COPD. CESD: Center for Epidemiological Studies Depression Scale; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; FRC: functional residual capacity; Sa_{O_2}: arterial oxygen saturation; 6MWD: 6-min walking distance: BODE: BMI, airflow obstruction, dyspnoea, exercise capacity; % LAA: percentage of low attenuation areas (*i.e.* emphysema) in the computed tomography; WBC: white blood cells; hsCRP: high-sensitivity C-reactive protein; IL: interleukin; TNF-α: tumour necrosis factor-α; CC-16: serum club cell secretory protein; CCL-18: chemokine C-C ligand 18; SPD: surfactant protein D; ICS: inhaled corticosteroids. [#]: 12 months prior to baseline; [¶]: lung volumes were only assessed in a subset of the ECLIPSE cohort at select sites, therefore, ~30% of group C patients and 21% of group D patients had lung volume data; [+]: post-bronchodilator; [§]: based on patient self-report.

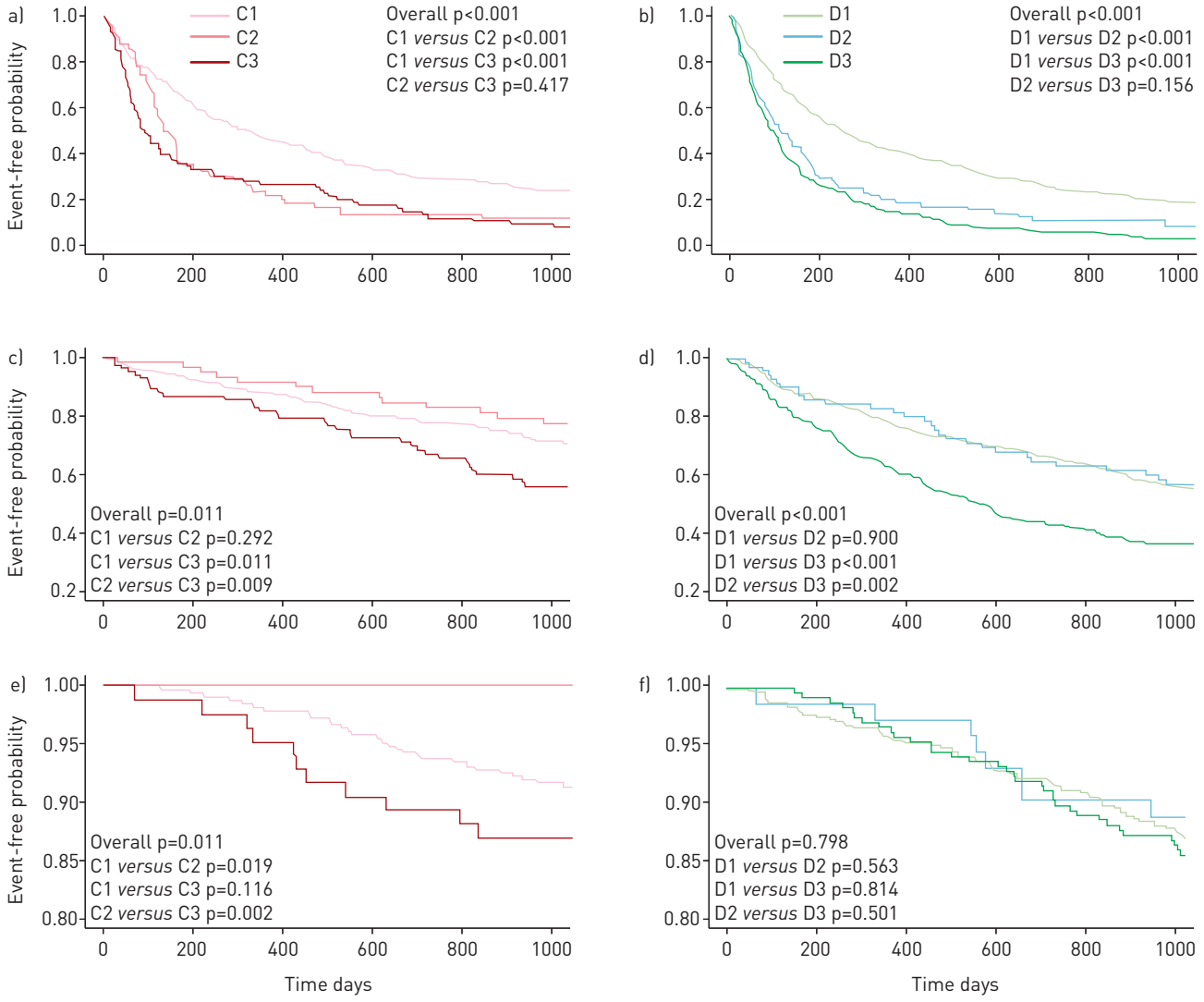

FIGURE 1 Kaplan–Meier curves for time to: a and b) moderate-to-severe exacerbations; c and d) time to hospitalisation for chronic obstructive pulmonary disease exacerbation; and e and f) all-cause mortality during follow-up in subgroups C1–C3 (a, c and e) and subgroups D1–3 (c, d and e).

predicted, 6MWD and the BMI, severity of airflow limitation, dyspnoea, exercise capacity (BODE) index were significantly associated with mortality. Similar factors, plus history of previous exacerbations, were significantly associated with hospitalisations in the two groups.

These results constitute one of the most detailed datasets of information on the characteristics and relationships with clinically relevant outcomes of the C and D GOLD subgroups available to date [2, 3]. Apart from the expected differences in FEV_1 and exacerbation rates in these different subgroups, it is of note that most variables were similar across them (table 1). However, a notable exception was that subgroups C2 and D2 had a higher prevalence of females (also noted by previous studies [3, 8]) and a lower severity of emphysema (table 1).

Our results confirmed previous observations indicating that a FEV_1 <50% reference alone (subgroups C1, D1) was the most frequent reason (~75% of patients) to classify them as group C or D [2–4]. This may have therapeutic implications since some C1 and D1 subgroup patients may benefit, mostly, from bronchodilator therapy, whereas C2/C3 and D2/D3 subgroups are likely to benefit most from the addition of anti-inflammatory therapy to reduce the risk of future exacerbations [9].

That exacerbations were more frequent in those subgroups defined as being at a high risk of an exacerbation, exclusively (subgroups C2 and D2) or partially (subgroups C3 and D3), by their previous history of frequent exacerbations (fig. 1) can be expected, since the strongest predictor of future exacerbations is the previous exacerbation rate [8]. In fact, Lange *et al.* [3] reported similar findings. Likewise, that the time to hospitalisation was significantly shorter in the C3 and D3 subgroups, but similar in the C1/C2 and D1/D2 subgroups (fig. 1), likely reflects the co-occurrence of two known risk factors for hospitalisation (*i.e.* severe

airflow limitation and frequent exacerbations) [10]. By contrast, it was of interest that all-cause mortality was highest in C3, intermediate in C1 and null in C2, whereas it was similar in D1, D2 and D3 (fig. 1f). Differences between C and D subgroups possibly reflect a more severe disease in the latter. On the other hand, the zero mortality during follow-up in the subgroup C2 patients is probably clinically relevant, although this could be due to the small sample size of this subgroup. Also of interest was the observation that the rate of exacerbations during follow-up was not different in subgroups C1 *versus* D1, C2 *versus* D2 or C3 *versus* D3, at variance with the rate of hospitalisation and mortality (except for subgroup C3 *versus* subgroup D3). Finally, as previously reported in the entire C and D groups [4], FEV_1 decline and the incidence of cardiovascular events or cancer during follow-up was similar across subgroups (table 1).

Several potential limitations of this analysis deserve comment. First, patients in the ECLIPSE study were treated according to their local physician, so these observations are not representative of a naïve COPD population. Likewise, there were treatment differences across groups, and these might have influenced outcomes by indication. Finally, most patients in the ECLIPSE study were recruited from referral centres, so results may not reflect COPD in the general population.

In summary, these results provide extensive information to better delineate the heterogeneity, both cross-sectional and longitudinally, of the C and D GOLD subgroups, which may be relevant for the design of new research aimed at optimising treatment in these high-risk COPD patients.

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The results of this study show that "high-risk" COPD patients (GOLD groups C and D) are highly heterogeneous http://ow.ly/LTMOv

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