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Determinants of poor 6-min walking distance in patients with COPD: The ECLIPSE cohort☆

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Summary
Background: The 6-min walking test (6MWT) is widely used to assess exercise tolerance in patients with chronic obstructive pulmonary disease (COPD). Given the prognostic significance of the 6MWT, it is important to identify why some COPD patients perform poorly in terms of this outcome. We aimed to identify clinical determinants of a poor 6-min walking distance (<350 m) in patients with COPD.
Methods: 1795 individuals with a diagnosis of COPD underwent spirometry; bio-electrical impedance analysis; low-dose computed tomography scans of the chest; 6MWT; ATS-DLD co-morbidity questionnaire; Center for Epidemiologic Studies of Depression Scale; COPD-specific St Georges Respiratory Questionnaire; modified Medical Research Council (mMRC) dyspnea scale as part of the baseline assessment of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study.

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Results: Patients with COPD have significant differences in performance in the 6MWT even after stratification for GOLD stages. Moreover, severe airflow limitation by GOLD stage, degree of emphysema by CT, oxygen use during/after the 6MWT, presence of depressive symptoms and moderate to severe symptoms of dyspnea (mMRC grade $\geq$2) are significant clinical determinants of poor 6MWD performance ($<$350 m).
Conclusions: The determinants of poor 6MWD are complex and depend on both physical (both pulmonary and non-pulmonary factors) and psychological factors as evaluated from a large multinational cohort of well-characterised patients with clinically stable moderate to very severe COPD.

Background

An impaired exercise tolerance is a cardinal clinical feature in chronic obstructive pulmonary disease (COPD), which cannot be confidently predicted from conventional descriptors of a COPD patient such as age, gender, forced expiratory volume in the first second (FEV_1) and body mass index (BMI).[1] For these reasons, it is essential to measure the patient's exercise tolerance.

The 6-min walking test (6MWT) is a practical, relatively simple test which has gained importance in evaluating the functional status of patients with COPD.[2] The test measures the distance walked with maximal intensity,[3] which better reflects the patient's functional exercise level for daily physical activities than do conventional lung function outcomes.[4,5]

The 6MWT is widely used in pulmonary rehabilitation programs[6] and in the evaluation of pharmacological and non-pharmacological treatments for COPD.[7–11] Indeed, 6MWT is recommended by the ATS/ERS as an important outcome measure in clinical trials.[12] Moreover, the 6MWT has been shown to predict mortality in patients with clinically stable COPD.[4,13,14] Indeed, walking distances $<$350 m on the 6MWT were associated with a significantly increased mortality.[4] In addition, the rate of decline in 6-min walking distance (6MWD) over time has been shown to continue in patients with severe COPD who cease to have significant changes in FEV_1[15] suggesting that the 6MWD can be used to follow a patient's worsening over time.

Given the prognostic significance of the 6MWT, it is important to identify why some COPD patients perform poorly in terms of this outcome. Many factors can influence 6MWD in COPD including gender,[16] body composition,[17] the degree of airflow limitation,[18] the degree of emphysema[19] and the rate of acute COPD exacerbations.[20] Moreover, perceptions of poor health (i.e., the degree of daily dyspnea,[21] emotional status[22] and health status[23]) correlate with 6MWD in COPD. Thus, the 6MWD seems to be an integrative test that reflects the physical, psychological and emotional capabilities of patients with moderate to severe COPD.

To date, it remains unknown whether and to what extent the above mentioned outcomes are interrelated in COPD. Therefore, with the large and comprehensive cohort of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study, we explored the importance of these factors relating to impairment of self-paced exercise performance together in a single study. Identifying clinical determinants of poor 6MWD may allow clinicians to better monitor and ameliorate impaired functional capacity in patients with COPD.

Methods

The current data are derived from the baseline assessments in the ECLIPSE study. The aims and operational aspects of the ECLIPSE cohort have been described elsewhere.[24] In brief, individuals (age: 40–75 years) were recruited to the study if they had a smoking history of $>$10 pack-years and a diagnosis of COPD.[25] All subjects performed baseline post-bronchodilator spirometry and the FEV_1% predicted was calculated.[26]

Body composition

Height (cm) and body weight (kg) were measured. Subjects also underwent bio-electrical impedance analysis (Bodystat 1500). Fat-free mass index was calculated using disease-specific equations.[27]

Computed tomography

Low-dose computed tomography (CT) scans of the chest (120 kVp, 40 mA, 1 or 1.25 mm slice thickness at full inspiration) were obtained to exclude non-COPD-related disease and to evaluate the severity and distribution of emphysema. The CT scans were evaluated centrally at the imaging unit at the University of British Columbia, Vancouver. The extent of emphysema was independently scored by 2 radiologists who were blind to the individual's lung function. Emphysema was reported as trivial, mild, moderate, and severe/very severe if it affected $<$5%, 5–25%, 25–50%, $>$50% of the lungs, respectively. A consensus reading was obtained when there was a difference of more than one emphysema category between the two observers. Otherwise, the average of the two readings was used in the analysis.

Six-minute walk test

The 6-min walk test was performed indoors, along a flat, straight, 30 m walking course supervised by a well-trained researcher according to the ATS guidelines.[2] A practice 6MWT was not completed. Patients were encouraged every minute of the 6MWT using two phrases: ''You are doing well'' or ''Keep up the good work''. Patients were allowed to stop and rest during the test, but were instructed to resume walking as soon as they felt able to do so. Patients

were asked to grade their shortness of breath and then their level of fatigue using a modified Borg scale specific for each at the beginning and at the end of the test.

Resting transcutaneous oxygen saturation was obtained before and after the 6MWT. Oxygen saturation before the 6MWT and the use of oxygen during and/or after the 6MWT was registered as possible determinants.

ATS respiratory questionnaire

Presence of self-reported cardiovascular co-morbidity was determined using the ATS-DLD questionnaire,[28] which was updated for the purpose of this study. An affirmative answer to one or more ''heart trouble'' questions (i.e., high blood pressure, angina, heart attack/myocardial infarction, stroke, heart failure, arrhythmia) was used as an affirmative for presence of cardiovascular co-morbidity. Presence of cardiovascular co-morbidity was examined as a possible determinant.

Depression questionnaire

All patients completed the 20-items, self-administered Center for Epidemiologic Studies of Depression Scale (CES-D) to assess the presence of depressive symptoms.[29] A total CES-D score can range from 0 to 60 points. Binary categories of respondents were created for this study using a generally accepted cut-off of $\geq$16 points indicative of a high load of depressive symptoms.[29]

Health status and mMRC dyspnea assessment

Health Status was assessed with the COPD-specific St Georges Respiratory Questionnaire (SGRQ-C).[30] The SGRQ-C total score and the SGRQ-C activity domain were used for the present analyses. In addition, dyspnea was assessed by the self-administrated modified Medical Research Council (mMRC) dyspnea scale.[31]

BODE index

The BODE index, a simple multidimensional grading system which identifies prognostically different patient subgroups, was determined using the algorithm proposed by Celli et al.[32] The BODE index was calculated as a characterizing variable and was not examined as a possible determinant as the index itself contains 6MWD as a component.

Statistics

Between-group comparisons were conducted by analysis of variance and Cochran–Mantel–Haenszel tests for continuous and categorical assessments, respectively. Logistic regression (with stepwise selection to determine model covariates) assessed individual predictors of poor walking distance (<350 m). The model was adjusted for age, height, weight, gender, and country which were assumed to be confounding variables. Model fit was evaluated by the Hosmer–Lemeshow goodness of fit test, examination of model residuals, and investigation of possible interactions. The confidence interval for area under receiver operating characteristic curve (AUC ROC) was computed by the method of DeLong.[33] Sensitivity and specificity were reported from the point on the ROC curve with the shortest distance from the upper left corner (0,1).

Results

Characteristics

Of a total of 2747 participants (COPD patients and (non-) smoking controls) enrolled into the ECLIPSE study,[24] 1795 patients with clinically stable COPD (63% men) from 12 countries completed the baseline 6MWT and were included in the current study. Patients generally had moderate to very severe COPD, a normal BMI, and an impaired health status (Table 1). Moreover, 27% of the patients with COPD had a high level of depressive symptoms (CES-D scale $\geq$16 points); 54% scored grade 2 or higher on the mMRC; and 54% reported the presence of cardiovascular disease(s).

Characteristics of patients with poor 6MWD

743 patients (41%) had a 6MWD <350 m (mean: 256 $\pm$ 73 m) while the remaining 1052 patients had a 6MWD $\geq$350 m (mean: 451 $\pm$ 81 m). The group of patients with a 6MWD <350 m had a higher proportion of women (41% vs. 34%); hospitalized exacerbations (12% vs. 6%); very severe emphysema (>50% emphysema by consensus radiologist read) (42% vs. 28%; Fig. 1); possible depression (37% vs. 20%); mMRC dyspnea grades of 2 or higher (77% vs. 38%); patient-reported cardiovascular disease(s) (59% vs. 50%); and oxygen users during 6MWT (16% vs. 3%) than was seen in subjects able to walk further (Table 1). Additionally, patients with a 6MWD <350 m generally had more severe airflow limitation (GOLD Stage IV: 23% vs. 7%; Table 1, Fig. 2) and worse health status (60 vs. 43 points on total SGRQ-C; and 77 vs. 55 points on the Activity domain of SGRQ-C). Comparable differences were still found between patients with 6MWD <350 m and $\geq$350 m for most outcomes after stratification for GOLD stages (Table 2).

Determinants of poor 6MWD

From the logistic regression analysis, GOLD stage 4 patients had a higher adjusted odds ratio for a poor 6MWD (<350 m) than GOLD stage 2 patients, OR 1.91 (95% CI 1.20–3.03), $p = 0.006$. Additionally, oxygen users during/after the 6MWT had an approximately doubling of risk of having a poor 6MWD than COPD patients without the use of oxygen, OR 2.16 (1.34–3.47), $p = 0.002$. Patients with mild emphysema or severe to very severe emphysema had a higher adjusted odds ratio for having a poor 6MWD than patients with trivial emphysema, OR 1.56 (1.07–2.27), $p = 0.020$; and 1.89 (1.29–2.78), $p = 0.001$, respectively. Finally, a mMRC dyspnea grade of 2 or higher (OR 2.24 (1.70–2.95), $p < 0.001$), a CES-D score of 16 points of higher (OR 1.51 (1.14–1.99), $p = 0.004$), lower inspiratory capacity (OR 0.97 (0.96–0.99), $p < 0.001$) and worse (higher) scores on the SGRQ-C Activity domain (OR 1.03 (1.02, 1.03), $p < 0.001$) were also independent predictors of a poor 6MWD in the present sample. The presence of patient-reported cardiovascular disease and a history of prior hospitalized exacerbation did not affect the odds of poor 6MWD (Table 3).

Table 1 Patient characteristics.

	All patients	<350 m walked	≥350 m walked	*p*-value
Patients	1795	743	1052	
Age yrs	63 ± 7	64 ± 7	63 ± 7	<0.001
Male	1135 (63%)	439 (59%)	696 (66%)	0.002
BMI kg/m^2	26 ± 6	27 ± 6	26 ± 5	<0.001
<21	264 (15%)	115 (15%)	149 (14%)	
21–30	1135 (63%)	417 (56%)	718 (68%)	
>30	396 (22%)	211 (28%)	185 (18%)	
FFMI kg/m^2	17 ± 3	17 ± 3	17 ± 3	NS
Prior hospitalized exacerbations	157 (9%)	91 (12%)	66 (6%)	<0.001
CVD by patient report	969 (54%)	439 (59%)	530 (50%)	<0.001
FEV_1 L	1.33 ± 0.52	1.14 ± 0.47	1.47 ± 0.50	<0.001
GOLD Stage				<0.001
Stage II	787 (44%)	228 (31%)	559 (53%)	
Stage III	765 (43%)	346 (47%)	419 (40%)	
Stage IV	243 (14%)	169 (23%)	74 (7%)	
Inspiratory capacity L	2.25 ± 0.73	2.00 ± 0.69	2.42 ± 0.71	<0.001
Extent of emphysema				<0.001
<5%	460 (26%)	151 (20%)	309 (29%)	
5–<25%	378 (21%)	143 (19%)	235 (22%)	
25–<50%	350 (19%)	137 (18%)	213 (20%)	
50–>75%	607 (34%)	312 (42%)	295 (28%)	
mMRC mean score	1.7 ± 1.1	2.2 ± 1.0	1.3 ± 0.9	<0.001
≥2	965 (54%)	570 (77%)	395 (38%)	<0.001
SGRQ-C Total Score	50 ± 20	60 ± 18	43 ± 19	<0.001
SGRQ-C Activity Score	64 ± 25	77 ± 20	55 ± 24	<0.001
CES-D Score	11.7 ± 9.3	14.2 ± 9.8	9.9 ± 8.5	<0.001
≥16	489 (27%)	278 (37%)	211 (20%)	<0.001
6MWD m	370 ± 124	256 ± 73	451 ± 81	<0.001
BODE Index	3.2 ± 2.1	4.8 ± 1.9	2.0 ± 1.4	<0.001
Patients requiring oxygen during/after 6MWT	154 (9%)	119 (16%)	35 (3%)	<0.001

m = meters; 6MWD = 6 min walk distance; BMI = body mass index; FEV_1 = forced expiratory volume in 1 s; CVD = cardiovascular disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = modified Medical Research Council Scale for dyspnea; CES-D = Center for Epidemiologic Studies Despression Scale; BODE Index = Airflow Obstruction, Dyspnea, and Exercise Capacity Index; NS = not significant. History of hospitalized exacerbation are those COPD exacerbations requiring hospitalization in the 12 months prior to patient entry in the ECLIPSE study as reported by the patient. All values are n (%) or mean ± standard deviation. †*p* values for difference between patients walking<350 m and ≥350 m.

The patients who used oxygen during/after the 6MWT had significantly different characteristics than patients who did not use oxygen during/after the 6MWT (Table 4).

Receiver operating characteristic curve

The area under the receiver operating characteristic (ROC) curve for the current model was 0.851 (0.834–0.869), with a sensitivity of 77.9% and a specificity of 77.5%.

Discussion

This large multinational study had two important findings: first, it showed that patients with COPD have significant differences in performance in the 6MWD even after stratification for GOLD stages. Second, we determined that the following covariates are significant clinical determinants of poor 6MWD performance (<350 m): severe airflow limitation by GOLD stage, degree of emphysema by CT, oxygen use during/after the 6MWT, presence of depressive symptoms and moderate to severe symptoms of dyspnea (mMRC grade ≥2).

Although poor 6MWD can be differentiated by increasing severity of GOLD stage (Table 3), there was considerable variation in the proportion of patients in each GOLD stage with a 6MWD <350 m or ≥350 m. For example, 29% of the GOLD stage 2 patients had a 6MWD <350 m, while 30% of the GOLD stage 4 patients had a 6MWD ≥350 m (Fig. 2). In addition, the identified clinical determinants from the regression model appear to be the same variables

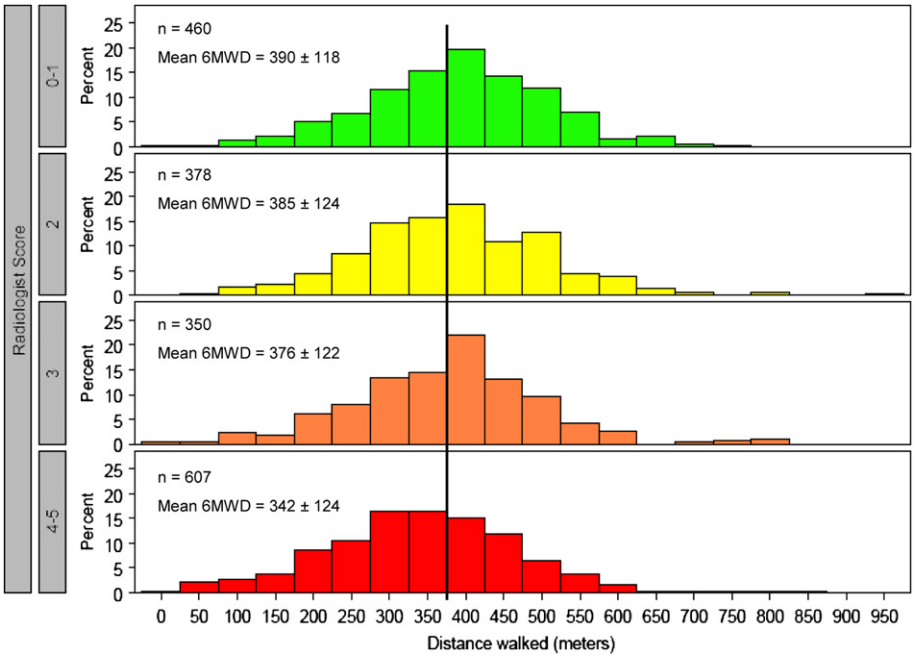

Figure 1 Histogram distribution of 6MWD by extent of emphysema. The bold line marks the <350 m walking distance threshold. The difference in the proportion of patients who walked <350 m between emphysema stages was statistically significant ($p < 0.001$).

differentiating the <350 m vs. ≥350 m walking groups in each GOLD stage (Table 2). These results suggest that the degree of airflow limitation only partially explains the variance in 6MWD in patients with moderate to very severe COPD, a finding previously suggested by other authors.[34,35] In fact, we found a similar number of pulmonary and non-pulmonary factors associated with a reduced 6MWT performance. Some of the non-pulmonary factors (mMRC dyspnea and depression scale) were more important or consistently associated with the distance walked compared to the pulmonary parameters investigated (inspiratory capacity and extent of emphysema). A decline in resting inspiratory capacity (incremental change of 200 ml) and the extent of emphysema only mildly to moderately increased the odds of having poor 6MWD, respectively (Table 3). Meanwhile, COPD patients with poor 6MWD had a worse mean SGRQ-C Activity score; a higher percentage of patients with symptoms of dyspnea (mMRC ≥ 2) and

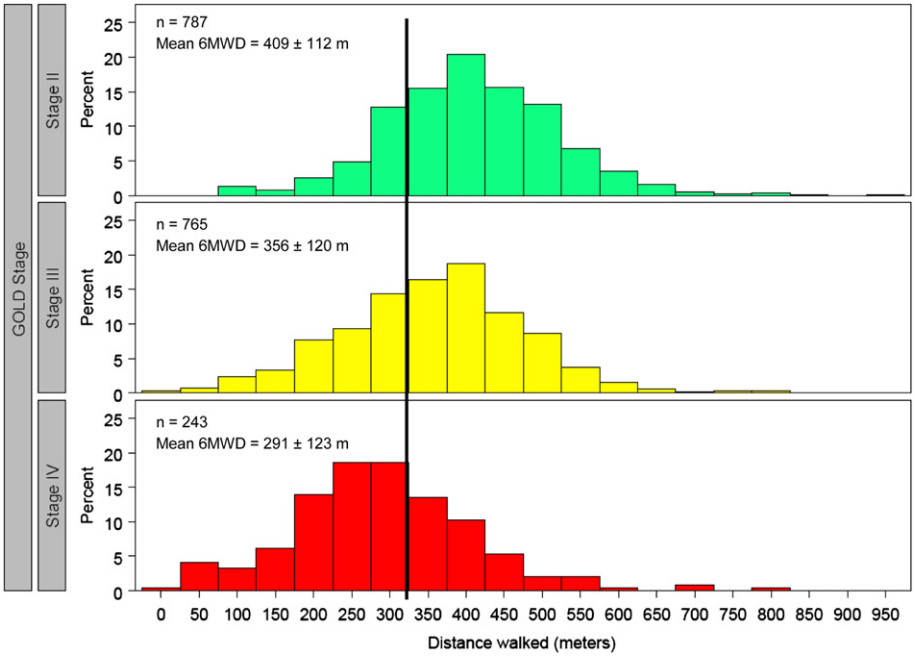

Figure 2 Histogram distribution of 6MWD by GOLD stage. The bold line marks the <350 m walking distance threshold. The difference in the proportion of patients who walked <350 m between GOLD stages was statistically significant ($p < 0.001$).

Table 2 Patient characteristics by GOLD Stage and 6MWD performance.

	Stage II		Stage III		Stage IV	
	<350 m	≥350 m	<350 m	≥350 m	<350 m	≥350 m
Patients	228	559	346	419	169	74
Age yrs	64 ± 7	63 ± 7	65 ± 7	63 ± 7	63 ± 7	61 ± 7
Male	119 (52%)	337 (60%)	202 (58%)	303 (72%)	118 (70%)	56 (76%)
BMI kg/m^2	29 ± 6	27 ± 5	27 ± 6	25 ± 5	25 ± 6	25 ± 5
<21	20 (9%)	59 (11%)	53 (15%)	76 (18%)	42 (25%)	14 (19%)
21–30	119 (52%)	390 (70%)	200 (58%)	277 (66%)	98 (58%)	51 (69%)
>30	89 (39%)	110 (20%)	93 (27%)	66 (16%)	29 (17%)	9 (12%)
FFMI, kg/m^2	18 ± 3	17 ± 3	17 ± 3	17 ± 3	16 ± 3	16 ± 2
Prior hospitalized exacerbations	15 (7%)	21 (4%)	46 (13%)	38 (9%)	30 (18%)	7 (9%)
CVD by patient report	150 (66%)	298 (53%)	198 (57%)	195 (47%)	91 (54%)	37 (50%)
FEV_1 L	1.62 ± 0.44	1.78 ± 0.45	1.04 ± 0.26	1.18 ± 0.26	0.70 ± 0.17	0.78 ± 0.15
Inspiratory Capacity L	2.39 ± 0.77	2.57 ± 0.74	1.90 ± 0.55	2.31 ± 0.64	1.69 ± 0.60	1.96 ± 0.55
Extent of Emphysema						
<5%	76 (33%)	222 (40%)	64 (18%)	76 (18%)	11 (7%)	11 (15%)
5–<25%	69 (30%)	135 (24%)	56 (16%)	90 (21%)	18 (11%)	10 (14%)
25–<50%	41 (18%)	113 (20%)	64 (18%)	86 (21%)	32 (19%)	14 (19%)
50–>75%	42 (18%)	89 (16%)	162 (47%)	167 (40%)	108 (64%)	39 (53%)
mMRC mean score	1.9 ± 1.0	1.1 ± 0.9	2.3 ± 1.0	1.5 ± 0.9	2.5 ± 1.0	2.0 ± 0.8
≥2	152 (67%)	163 (29%)	277 (80%)	178 (42%)	141 (83%)	54 (73%)
SGRQ-C Activity Score	69 ± 22	48 ± 24	79 ± 19	61 ± 22	85 ± 16	72 ± 17
CES-D Score	14 ± 10	10 ± 9	15 ± 10	10 ± 8	14 ± 10	10 ± 8
≥16	82 (36%)	109 (19%)	135 (39%)	87 (21%)	61 (36%)	15 (20%)
6MWD m	282 ± 59	460 ± 84	252 ± 74	442 ± 73	229 ± 78	431 ± 87
BODE Index	3.0 ± 1.3	1.1 ± 0.9	5.3 ± 1.4	3.0 ± 1.0	6.4 ± 1.4	4.2 ± 0.9
Patients requiring oxygen during/ after 6MWT	11 (5%)	12 (2%)	52 (15%)	17 (4%)	56 (33%)	6 (8%)

m = meters; 6MWD = 6 min walk distance; BMI = body mass index; FEV_1 = forced expiratory volume in 1 s; CVD = cardiovascular disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = modified Medical Research Council Scale for dyspnea; CES-D = Center for Epidemiologic Studies Depression Scale; BODE Index = Body Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index; NS = not significant. History of hospitalized exacerbation are those COPD exacerbations requiring hospitalization in the 12 months prior to patient entry in the ECLIPSE study as reported by the patient. All values are *n* (%) or mean ± standard deviation.
[†]*p* values for difference between patients walking <350 m and ≥350.

depressive symptoms (CES-D ≥ 16) (Table 1) which remained after stratification for GOLD stages (Table 2) and after correction for gender, age, body weight and country (Table 3). All three self-perceived measures identified an increased likelihood of having a poor 6MWD (Table 3). Therefore, it seems reasonable to conclude that the presence of poor 6MWD is multifactorial and that non-pulmonary outcomes should be considered to explain the variance in 6MWD in patients with moderate to very severe COPD.

Surprisingly, fat-free mass (FFM) index, hospitalized COPD exacerbations (self-reported in the previous year before enrolment in the study), and presence of cardiovascular disease did not differentiate themselves as determinants of a poor 6MWD which is somewhat contrary to the published literature. However, there are several possible reasons which may explain these findings. In the present study the mean FFM index was identical between COPD patients with and without poor 6MWD (Table 1) and ultimately FFM index was not selected by the model as a determinant of poor 6MWD, after correction for confounding variables (Table 3). In contrast, Ischaki and colleagues reported a positive correlation between 6MWD and FFM index in patients with COPD, however this was demonstrated without correction for confounding variables like weight, gender, age and the degree of airflow limitation.[17] Addition of these variables in the model along with the inclusion of a number of other factors which were relatively more significant to poor 6MWD explain why FFM index was not selected by the stepwise regression model. Also in our study, a higher proportion of the COPD patients with poor 6MWD had self-reported hospitalizations for COPD exacerbations (Table 1), however previous hospitalized exacerbations did not reach statistical significance as a determinant of poor walk distance (Table 3). We know from the literature that COPD patients with a lower 6MWD are more likely to have exacerbations following pulmonary rehabilitation, and that acute COPD exacerbations are associated with clinically relevant reductions in 6MWD.[20,36,37] The reason that statistical significance was not achieved in the present

Table 3 Odds ratios between subject characteristics and poor 6MWT performance (<350 m) — Logistic Regression.

	<350 m walked	
	OR (95% CI)	*p*-value
GOLD Staging		
Stage II	1.00	
Stage III	1.10 (0.82, 1.48)	NS
Stage IV	1.91 (1.20, 3.03)	0.006
Inspiratory Capacity (per 200 ml)	0.97 (0.96, 0.99)	<0.001
Oxygen during/after walk		
No	1.00	
Yes	2.16 (1.34, 3.47)	0.002
Extent of Emphysema		
<5%	1.00	
5—<25%	1.56 (1.07, 2.27)	0.020
25—<50%	1.35 (0.91, 2.00)	NS
50—>75%	1.89 (1.29, 2.78)	0.001
Cardiovascular disease		
No	1.00	
Yes	1.11 (0.86, 1.43)	NS
History of Hospitalized Exacerbation		
No	1.00	
Yes	1.47 (0.97, 2.25)	NS
mMRC		
<2	1.00	
≥2	2.24 (1.70, 2.95)	<0.001
CES-D		
<16	1.00	
≥16	1.51 (1.14, 1.99)	0.004
SGRQ-C activity domain	1.03 (1.02, 1.03)	<0.001

OR = odds ratio (adjusted for country, age, height, weight, and gender); 95% CI = 95% confidence interval; NS = not significant. The < 350 m odds ratio reflects the odds of walking <350 m vs. ≥350 m. History of hospitalized exacerbation are those COPD exacerbations requiring hospitalization in the 12 months prior to patient entry in the ECLIPSE study as reported by the patient.

Table 4 Characteristics of patients with or without oxygen during/after 6MWT.

	No oxygen	Oxygen during/ after 6MWT	*p*-value[†]
Patients	1641	154	
Age yrs	63 ± 7	65 ± 6	<0.001
Male	1040 (63%)	95 (62%)	0.678
BMI kg/m^2	26 ± 5	27 ± 6	0.053
FFMI kg/m^2	17 ± 3	17 ± 3	0.657
Prior hospitalized exacerbations	131 (8%)	26 (17%)	<0.001
CVD by patient report	877 (53%)	92 (60%)	0.134
FEV_1 L	1.37 ± 0.51	0.94 ± 0.40	<0.001
GOLD stage			<0.001
Stage II	764 (47%)	23 (15%)	
Stage III	696 (42%)	69 (45%)	
Stage IV	181 (11%)	62 (40%)	
Inspiratory capacity L	2.29 ± 0.72	1.83 ± 0.68	<0.001
Extent of emphysema			<0.001
<5%	454 (28%)	6 (4%)	
5—<25%	354 (22%)	24 (16%)	
25—<50%	317 (19%)	33 (21%)	
50—>75%	516 (31%)	91 (59%)	
mMRC mean score	1.6 ± 1.0	2.2 ± 1.0	<0.001
≥ 2	852 (52%)	113 (73%)	<0.001
SGRQ-C total score	49 ± 20	61 ± 15	<0.001
SGRQ-C activity score	62 ± 25	82 ± 17	<0.001
CES-D score	11.5 ± 9.3	13.8 ± 9.2	0.003
≥16	434 (26%)	55 (36%)	0.014
6MWD m	379 ± 120	271 ± 116	<0.001
BODE Index	3.0 ± 2.1	5.1 ± 2.1	<0.001

study may have been due to adjustments made for confounding variables in the model, which like patient body weight, have been shown to be clinical determinants of hospitalized acute COPD exacerbations.[36] Moreover, in our study, only patients with clinically stable COPD were eligible to participate;[24] and the exacerbation-related hospitalizations were based solely on patient recall of events 1-year prior to beginning the ECLIPSE study. In a similar fashion to hospitalized COPD exacerbations, self-reported cardiovascular diseases was not a significant determinant of a poor 6WMD, although it was commoner in patients with poor 6MWD in GOLD stages 2 and 3 ($p \leq 003$), but not in GOLD stage 4 patients ($p = 0.581$). As before, this may be explained in part by the ECLIPSE study requirement for ''stable'' co-morbid conditions at the start of study participation.[24]

Taken together, this report has several strengths. It includes a large, multinational population of patients with different levels of disease severity, and a high proportion of women. The simultaneous analysis of several factors previously reported to affect the 6MWT allowed to determine the interrelation among them and selection of seven distinctive ones. The identified predictors were shown to demonstrate good discrimination between COPD patients with and without a poor 6MWD (area under the ROC curve of 0.851). Although very good, it may be speculated that some other factors not included in our model could even further improve its discriminative power (e.g., measurement of daily physical activity levels,[5] systemic biomarkers of biological aging[38] and systemic inflammation[39]).

A 6MWD <350 m was used as a poor walk distance threshold in the present study based upon previous work demonstrating association with mortality in patients with COPD.[4] Nevertheless, it will still be important to replicate these outcome-based findings from the 3-year prospective ECLIPSE cohort data. Moreover, it will be of clinical importance to assess whether 6MWD will decline over time and whether and to what extent clinical predictors of decline selected in this analysis would be of value during the 3 years of follow-up of the ECLIPSE cohort. This information is of critical value to better assess the 6MWT as a potential outcome to be measured in pharmacologic intervention studies. Its association to the

systemic repercussion of the disease (cardio-pulmonary, perception and psychological impact) and mortality should complement spirometry, which to date has been the only important parameter to modify in COPD.

To conclude, the determinants of poor 6MWD are complex and depend on both physical (both pulmonary and non-pulmonary factors) and psychological factors as evaluated from a large multinational cohort of well-characterised patients with clinically stable moderate to very severe COPD. This could in time result in better non-pharmacological as well as pharmacological management of patients with COPD. Indeed, poor 6MWD may improve in patients with moderate to very severe COPD without clinically relevant changes in pulmonary function.[8] So, from a patient management perspective, we hypothesize that GOLD stage 2 patients with a poor 6MWD should be evaluated more critically to determine whether pharmacological or non-pharmacological treatment interventions are likely to be helpful. It seems that this group may be more likely to benefit from interventions targeting extra-pulmonary manifestations of COPD as opposed to interventions targeting pulmonary function.

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Conflict of interest statement

Jørgen Vestbo has recieved honoraria for lectures and/or advisory board meetings from GSK, AstraZeneca, Boehringer-Ingelheim, Pfizer, Nycomed, Hoffmann-La Roche and Talecris. Peter M.A. Calverley has advised GSK, Boehringer Ingelheim and AstraZeneca on clinical trial design and conduct; and received honoraria from GSK, AZ and Nycomed for speaking about COPD in general. No direct overlap with this paper. Funds from Boehringer Ingelheimand Nycomed for unrelated studies and GSK to fund this research. Michael L Watkins, Lisa D. Edwards and Ruth Tal-Singer are employed by GSK (sponsor of the ECLIPSE trial). Martijn A. Spruit, Victor Pinto-Plata, Bartolome R. Celli and Emiel F.M. Wouters have no conflict to declare.

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