Evaluation of criteria for clinical control in a prospective, international, multicenter study of patients with COPD

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ABSTRACT

Background: The concept of clinical control in COPD has been developed to help in treatment decisions, but it requires validation in prospective studies.

Method: This international, multicenter, prospective study aimed to validate the concept of control in COPD [control= stability (no exacerbations or impairment in CAT scores) + low impact (low level of symptoms)]. We investigated the level of control, compared characteristics of patients according to the control status, and performed a sensitivity analysis of the levels of control using either clinical criteria or questionnaires (COPD Assessment Test –CAT- or Clinical COPD Questionnaire –CCQ-).

Results: A total of 314 patients were analysed (mean age 68.5 years and mean FEV1(%)= 52.6%). According to the prespecified criteria 21% of patients were classified as controlled, all of them with mild/moderate COPD (Body mass index, Obstruction, Dyspnea and Exacerbations, –BODEx- index <5). A high level of dyspnea, a high CAT score or an exacerbation in the previous 3 months were found, using univariate analysis, to be the main reasons for patients not being classified as controlled. Multivariate analysis showed that female sex, chronic bronchitis and having exacerbations in the previous year were associated with uncontrolled COPD. Changing the severity cut off of BODEx from 5 to 3 did not change significantly the percentage of patients fulfilling the criteria of control.

Conclusions: The proposed criteria of control were only fulfilled by 21% of patients. The suggested cut offs and their predictive value for poor outcomes need to be refined in prospective studies.

KEYWORDS: COPD; control; CAT; CCQ; Outcomes.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition requiring therapeutic management to be tailored to the clinical characteristics and disease severity of the individual patient (1,2). Treatment of COPD should be aimed at controlling symptoms and reducing the risk of exacerbations (3,4); if these objectives are achieved we could consider that the disease is under control, regardless of the degree of impairment in lung function or health status (5).

Unfortunately, even with pharmacological and non-pharmacological treatment strategies, patients with COPD usually have daily symptoms and suffer exacerbations of the condition (6); therefore, there is a need for objective measures to evaluate the level of control of the disease. The concept of control has been well developed in asthma (7), however, in COPD the different characteristics of the disease have made this concept elusive. Objective physiological measures of lung function and multicomponent indices are very helpful in evaluating the stage of the disease and establishing a prognosis (8), and the use of patient reported outcomes (PROs) helps us to understand the impact of the disease on health-related quality of life, sleep quality and mood, among others (9); however, these measures are not sensitive enough to guide treatment decisions.

It is well known that patients with the same level of lung function impairment may have very different symptom burdens, or patients with the same health status may have different risks of exacerbations (10); therefore, the concept of control should incorporate the main objectives of treatment of COPD: reduction in symptoms and reduction in exacerbation risk. Recently, it has been proposed that control in COPD reflects the impact and stability of the condition (5,11). Impact is related to the manifestations of the disease at the time of medical consultation and stability is related to the changes of the clinical status of the patient over time, including the presence of exacerbations.

Control in COPD would be a conceptual dimension requiring demonstration of both low impact and clinical stability of disease. The developers of the concept hypothesize that patients who have controlled COPD will have better clinical outcomes (reduced frequency of exacerbations and mortality, and improved health-related quality of life), as well as a slower decline in lung function and reduced COPD-related healthcare costs.

The current study was designed with the objective to validate the concept of control as a valid and reliable prognostic measure. In the current work, we present the design of the study, the baseline characteristics of the population and their control status according to the proposed criteria, along with the changes in control status when the criteria for impact and/or stability are modified.

METHOD

Study design

This international, multicenter, prospective study of a cohort of patients with COPD aimed to validate the concept of clinical control in COPD. It was a 21 month prospective observational study, comprising 5 evaluation points: one screening evaluation (V-1), one baseline visit after 3 months (V0) and 3 follow-up visits at 6 months intervals (V1-V3). At screening visit, eligible patients had a full clinical assessment, including evaluation of: current smoking status, presence of comorbidities, spirometry and baseline questionnaires. At baseline visit, the control status of the patients was assessed as indicated below. Throughout the study, patients were managed according to the criteria of the investigators.

The primary study outcome is the difference in (annualized) rates of a composite endpoint for patients controlled versus uncontrolled at baseline, and will be measured over the 18-month follow-up period. The composite endpoint is defined as occurrence of any of the

following: an ambulatory exacerbation, an emergency room attendance or hospital admission due to an exacerbation, or death.

In this work, we present the results of V-1 and V0 visits in terms of baseline characteristics of the included patients, the levels of clinical control according to the prespecified criteria, and the comparison of characteristics of patients according control status. A sensitivity analysis of the levels of control was performed using either clinical criteria or questionnaires, and after modifying the classification of severity of COPD at screening.

This study was conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (e.g. European Union [EU] Directive 2001/20/EC and 2005/28/EC). The study was approved by the local Research and Ethics Committees of each participating research site and all patients provided written informed consent. The data for UK was obtained from the Optimum Patient Care Research Database (OPCRD) and permission to access and link UK data to anonymous electronic medical records was obtained from the Health Research Authority for clinical research use (REC reference 15/EM/0150). This study was registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), Register Number EUPAS10679.

Population

Eligible patients had to have spirometry-defined COPD (i.e. post-bronchodilator FEV1/FVC<0.7), be over 40 years of age, be current or ex-smokers with at least 10 pack-years of smoking exposure, and be in a stable clinical state (as judged by the investigator) at point of recruitment. Patients were excluded from the trial if any of the following were true, they: 1) Had any chronic concomitant respiratory condition other than asthma or bronchiectasis (e.g. cystic fibrosis, lung fibrosis); 2) Had severe comorbidity with a life expectancy shorter than 2 years; 3) Were unable to understand the instructions of the study

or to fill in the questionnaires; 4) Were unwilling to sign the informed consent; 5) Were participating in another clinical study or clinical trial.

Measurements

The prespecified criteria of clinical control were described by Soler-Cataluña et al. (5,11). Briefly, a patient was considered controlled when disease was clinically stable and of low impact, when adjusted for the level of disease severity. Stability was defined by the absence of exacerbations in the previous 3 months plus stability in the COPD Assessment Test (CAT), defined as any change that was less than a 3 unit increase (12). For comparison, we also considered a change in the Clinical COPD Questionnaire (CCQ) scores of 0.4 units or less as an alternative criterion for stability (13). Impact was classified as low or high according to the information collected on sputum (presence and colour), breathlessness, daily physical activity and (patient reported) rescue medication. In summary, "controlled" was defined as:

1) "low impact", based on clinical symptoms and CAT score (Table 1),

AND

2) "stable", defined as no exacerbations and no substantial increase (>3 units) in CAT score in the previous 3 months.

Evaluation of impact was adjusted by disease severity according to the Body Mass Index, Obstruction, Dyspnea, and Exacerbations (BODEx) indices (14). Patients with BODEx 4 or less were classified as mild/moderate and those with 5 or more as severe.

The control status of the patients was established according to the clinical and questionnaire data obtained at baseline visit (V0) and the history of exacerbations and changes in questionnaires' scores between screening visit (V-1) and V0.

The CAT is a specific questionnaire that measures the impact of disease in a patient using 8 questions which evaluate cough, expectoration, dyspnea, chest tightness, patient confidence,

limitations in daily activities, quality of sleep and energy. The CAT score ranges from 0 to 40, and the higher the score the worse the health status of the patient (15). The CCQ has three domains: symptoms (4 items), functional status (4 items) and mental state (2 items), graded on a 7-point Likert scale from 0 to 6 (0=no impairment) (16). Breathlessness was measured by the modified Medical Research Council (mMRC) dyspnea scale (17) and physical activity by self-declared minutes walking per day, as previously described (18). Comorbidities were assessed with the age-adjusted Charlson index (19).

A COPD exacerbation was defined as of any one of the following: acute use of oral corticosteroids and/or a course of antibiotics, for lower respiratory symptoms or within 5 days of an unscheduled hospital admission/ emergency department attendance for acute respiratory symptoms.

Statistical analysis

The sample size calculation was based on a previous pilot study in tertiary hospitals in Spain, in which 55% of patients with COPD were controlled based on the proposed criteria (unpublished data). We performed a conservative approach using the expected frequency of exacerbations according to results from the ECLIPSE Study, in which the annualized rate of exacerbations was 1.2 per patient (20). We hypothesize that, in controlled COPD patients, this annual rate could be 40% lower (0.72 per patient). Accepting an alpha risk of 5% and a beta risk of 10% in a two-sided test, a total of 285 COPD patients will be necessary to find this annualized incidence ratio difference statistically significant between controlled and uncontrolled patients. With an expected drop-out rate of 15%, a total of 328 patients should be enrolled in the study. Sample size has been calculated with !NI2IS macro (SPSS V23).

Absolute frequencies and percentages were used for comparisons of qualitative variables. The description of quantitative variables was performed using the mean and standard deviation (SD). The Kolmogorov-Smirnov test was used to assess the normality of

distributions. In the case of quantitative variables, the comparison of the characteristics between controlled versus uncontrolled patients was carried out using the Student t-test (Mann-Whitney U-test if normality was not assumed). The Chi-squared test (Fisher test for frequencies <5) was employed for the comparison of categorical variables.

A predictive model was developed using backward stepwise logistic regression analysis including control as a dependent variable. Clinical and demographic variables, not related to the definition of control and with a significance level <0.2 in the univariate analysis, were included as independent variables. The results are reported with odds ratios (OR) with a 95% confidence interval (CI) and *p*-values. The Hosmer-Lemeshow goodness-of-fit test was performed to assess the overall fit of the model. For all tests, *p*-values <0.05 were considered statistically significant. All analyses were performed using SPSS (V 23).

A sensitivity analysis of the control criteria was performed. The differences in the frequency of control according to different criteria for impact and/or stability were investigated. Impact was defined by using only clinical criteria, CAT or CCQ scores and the combinations of clinical criteria plus either CAT or CCQ scores. Stability was defined by the history of exacerbations alone or changes in CAT or CCQ scores, or combinations of history of exacerbations plus either changes in CAT or CCQ. All these possibilities were compared with the prespecified definition: impact by clinical criteria and stability by history of exacerbations and changes in CAT scores.

RESULTS

Population

A total of 349 patients were recruited, of which 314 (90%) completed the baseline visit and could be evaluated for control status and constitute the population of this study. The mean age was 68.5 years [standard deviation (SD)= 8.7], 47 (15%) were managed in primary care

and the remaining patients in specialized centers, 72.5% were male and mean FEV1 was 52.6% of predicted (18). A total of 276 (87.8%) were classified as having mild/moderate COPD and 39 (12.2%) as severe based on the BODEx index. The characteristics of the population are described in Table 2.

Control status, characteristics and treatment of controlled and uncontrolled patients

A total of 67 (21%) of patients fulfilled the criteria of control, all of them classed as having mild/moderate disease. Comparison of characteristics of controlled versus uncontrolled patients are presented in Table 2. Uncontrolled patients were more frequently female, with more comorbidities, more chronic bronchitis, more exacerbations the previous year and worse FEV1.

Regarding pharmacological treatments, uncontrolled patients were more frequently using inhaled corticosteroids (ICS), in particular as part of triple therapy (Long-acting beta-2 agonist (LABA)/ICS/long-acting antimuscarinic agent (LAMA)) (Table 3).

Factors accounting for uncontrolled status of patients.

Uncontrolled status may be due to high impact and/or instability of disease. We analysed the number of patients that were classified as high impact based on the different clinical criteria and questionnaire scores. mMRC was the most frequent criterion not fulfilled by patients (36.7% of mild/moderate and 84.6% of severe patients). More than half of the patients of both degrees of severity did not fulfil the criteria of control for the CAT score (Table 4).

Similarly, we evaluated the number of patients that were classified as instable based on the presence of exacerbations or large changes in questionnaire scores between V-1 and V0. Up to 51.2% of severe and 17.7% of mild/moderate patients experienced an exacerbation in the previous 3 months and were therefore not considered stable. Regarding CAT, 31.7% and

38.4% of mild/moderate and severe patients, respectively, experienced a change in CAT scores greater than the prespecified threshold (Table 4).

Factors associated with control. Multivariate analysis

A backward logistic multivariate model was developed with control as independent variable, and clinical and demographic variables, not related to the definition of control, as dependent variables. The adjusted model showed that male sex, absence of chronic bronchitis and no exacerbations in the previous year were independently and significantly associated with control (Table 5). This model showed good goodness-of-fit (Lemeshow p=0.825).

Sensitivity analysis: Impact of using different criteria for impact and stability

No large changes in the frequency of controlled patients were observed in the sensitivity analysis with different criteria for impact and stability, based either on clinical symptoms or questionnaire scores. The percentage of control ranged from a minimum of 13% with the more stringent criteria to a maximum of 32% compared with 21% with the prespecified criteria.

When patients were classified as severe based on a BODEx index of 3 or more, the percentage of controlled patients similarly ranged from 17% to 37% (Table 6).

DISCUSSION

Our study is the first attempt to prospectively evaluate the validity of the concept of control of COPD for clinical practice. In the current analysis, we have observed that the proposed criteria for control were very restrictive; only 21% of a group of patients with COPD of different degrees of severity, 85% of which were followed in specialized centers, fulfilled the criteria required to be considered controlled. In the mild/moderate subgroup of patients approximately two thirds did not fulfil the clinical criteria of low impact and 42% were classified as unstable; therefore only around one quarter were defined as controlled.

Regarding severe patients, only one out of 39 was considered to have a low impact and finally no patients could be classified as controlled. Interestingly, changing the threshold of severity from 5 to 3 in the BODEx index did not change significantly the number of patients that fulfilled the criteria of control. Female sex, presence of chronic bronchitis and having exacerbations in the previous year were significantly and independently associated with uncontrolled status.

These results are similar to those obtained in a retrospective analysis of the Optimum Patient Care Research Database (OPCRD) in the UK (21). Using the scores of the CAT questionnaire and some proxies for the clinical criteria of impact, only 4.5% of that primary care population of patients with COPD could be classified as controlled. Interestingly, controlled patients had a significantly reduced risk of future exacerbations, suggesting that the concept of control is valid as a predictor of poor outcomes (21). In the present analysis we explored the characteristics of controlled versus uncontrolled patients and the impact of different criteria for the classification of control; however, the final validation of the best criteria for clinical control will require the evaluation of the complete follow-up of the cohort.

Soler-Cataluña et al. (5) proposed the concept of control of COPD to help in clinical decisions about treatment of the disease. This new concept was composed of: a) the impact of the disease on the patient at the time of consultation measured by the level of symptoms, the use of rescue medication and the level of regular physical activity, or alternatively with the use of a short questionnaire (CAT or CCQ), and b) the stability measured by the changes in the questionnaire scores (either CAT or CCQ) and exacerbations in the previous 3 months.

These easy to obtain measurements should be predictive of future outcomes and sensitive enough to change with therapy. In order to validate the concept of control and establish the best thresholds for impact and stability, this prospective, international study was conducted.

From the analysis of the baseline data, we can conclude that the proposed criteria require some refinement, in particular for severe patients. The thresholds of physical activity and rescue medication seem to be well calibrated, since only around one third of patients did not reach that level. However, 84% of severe patients were classified as high impact due to the criterion of dyspnea. Similarly, the cut offs suggested for CAT and CCQ scores seem to be very restrictive as less than 50% of patients could be considered as having low impact according to their questionnaire scores. Although the CAT score has been demonstrated to be the best predictor of the risk of future exacerbations compared with other PROs (22), the best threshold for increased risk is yet to be defined (23,24). In the previous database study using the OPCRD, the authors could not identify a value of the CAT score with enough predictive value for future exacerbations (21). The results of the follow-up of the current study may help us to identify a cut off CAT score that provides a measure of low/high clinical impact with prognostic implications. The suggested change of 2 units in the CAT score as a threshold of stability was considered based on the identification of the minimum clinically important difference (12); however, Pothirat et al. (25) suggested a change of 4 units as the optimum cut off point score for the detection of acute deterioration in health status with a sensitivity, specificity and accuracy of 76.8%, 83.6% and 82.4%, respectively. Similarly, a change of less than 4 units in the CAT score from admission to discharge was significantly and independently associated with increased risk of clinical failure in the three months following discharge of exacerbated COPD patients (26). Previous work in over 3,700 patients has suggested that for every 10 point worsening of CAT score there is a 28% greater risk of 2 or more exacerbations in the following year (27). New prospective studies

may help to establish the best cut off for changes in CAT scores as a predictor of poor outcomes in COPD.

An individual analysis of the predictive value of the different proposed clinical criteria is also required. Sputum is the variable that has shown a lowest discriminative property for the level of impact. In contrast, having chronic bronchitis was associated, in multivariate analysis, with a lower probability of control. Chronic bronchitis is a well recognized risk factor for exacerbations (28) but the future risk associated with the quantity and characteristics of sputum during the clinical visit may not be significant or may be irrelevant in the context of the other proposed criteria for impact.

In addition to chronic bronchitis, female sex and having exacerbations the previous year were identified as variables significantly associated with uncontrolled status in multivariate analysis. It has previously been reported that women with COPD present with more symptoms and worse health status compared with men with similar degree of airflow obstruction (29). History of previous exacerbations is also associated with worse health status (30) and is the best predictor of future exacerbations (20).

We performed an exploratory sensitivity analysis to investigate the changes in the percentage of controlled patients following the changes in the criteria used for impact and stability. According to the prespecified criteria; i.e. low impact by clinical criteria and stability based on the absence in exacerbations and stability in the CAT score, only 21% of patients were classified as controlled, all of them with mild/moderate disease. Using more restrictive criteria requiring low impact by both clinical criteria and low CAT or CCQ scores, only 13% could be considered controlled. On the contrary, when only CAT scores were used to evaluate low impact and stability, up to 32% of patients reached the threshold of control, exactly the same 32% were classified as controlled when impact was based on clinical criteria and stability only on the absence of exacerbations in the previous 3 months.

Interestingly, these percentages did not change significantly when the severity of patients was classified with a cut off of 3 instead of 5 in the BODEx index, indicating that the low percentage of controlled patients was not related to the classification of severity. Alternatively, it can be speculated that there is no significant difference in the severity or prognosis between BODEx 3 and 5, and therefore other cut offs should be explored in the future.

CONCLUSIONS

In conclusion, the current proposed criteria for clinical control of COPD appear to be too restrictive. Changes in the classification of severity of COPD based on the BODEx index have very limited influence in the classification of controlled patients. In contrast the pre-specified cut offs of symptoms, physical activity and questionnaire scores may require refinement based in the results of the prospective follow-up phase of the study.

DECLARATION OF INTEREST

MM has received speaker fees from Boehringer Ingelheim, AstraZeneca, Chiesi, GlaxoSmithKline, Menarini, Teva, Grifols and Novartis, and consulting fees from Boehringer Ingelheim, GlaxoSmithKline, Gebro Pharma, CLS Behring, Cipla, MediImmune, Mereo Biopharma, Teva, Novartis and Grifols.

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CK Rhee received consulting/lecture fees from MSD, AstraZeneca, Novartis, GSK, Takeda, Mundipharma, Sandoz, Boehringer-Ingelheim, and Teva-Handok.

RWC has board membership with GSK, Aerogen, Novartis, and Teva Pharmaceuticals; consultancy agreements with, Aerogen, GlaxoSmithKline, Novartis, Teva Pharmaceuticals,

and Vitalograph as well as grants and unrestricted funding for investigator-initiated studies from Vitalograph, Aerogen and GlaxoSmithKline.

BA reports personal fees and grants from Novartis AG, personal fees from Boehringer-Ingelheim, personal fees from GSK, personal fees from Aztra-Zeneca, grants and personal fees from Menarini, outside the submitted work;

JJSC has received speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Esteve, Ferrer, GSK, Menarini, Novartis, and Pfizer, and and consulting fees from AirLiquide, Boehringer Ingelheim, Chiesi, GSK, AstraZeneca, Ferrer and Novartis.

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AT has participated as a member of the local COPD advisory board for Astra Zeneca, GlaxoSmithKline, Bayer, Takeda and Novartis and has received meeting/conference travel grants from Boehringer Ingelheim, Novartis, Astra Zeneca and GlaxoSmithKline.

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Table 1. Criteria used to define low/high impact in COPD based on clinical data and scores of CAT or CCQ questionnaires.

	Mild to moderate severity (BODEx ≤ 4 points)		**Severe/very severe COPD (BODEx ≥ 5 points)**	
	Low impact	**High impact**	**Low impact**	**High impact**
Clinical evaluation:				
Dyspnea (mMRC)	0 – 1	≥ 2	0 - 2	≥ 3
Rescue medication	≤ 3 times in the last week	> 3 times in the last week	≤ 2 times a day	> 2 times a day
Daily physical activity* (time walked per day)	≥ 60 min	< 60 min	≥ 30 min	< 30 min
Sputum color	Absent or White	Dark	Absent or White	Dark
Questionnaires:				
- CAT	≤ 10	>10	≤ 20	>20
- CCQ	≤ 1	>1	≤ 2	>2

Footnote: mMRC: modified Medical Research Council; CAT: COPD assessment test; CCQ: clinical COPD questionnaire

Table 2. Demographic and clinical characteristics of the population and comparison between controlled and uncontrolled patients.

	All (n=314)	**Controlled (n=67)**	**Uncontrolled (n=247)**	**P value**
Age, years	68.5 (8.7)	67.9 (8.5)	68.7	0.53
Sex, men (%)	225 (72.5)	58 (89.2)	167 (68.1)	0.001
Living status (%):				
Alone	60 (19.3)	8 (12.3)	52 (21.1)	0.09
Couple or relatives	248 (80)	56 (86.5)	192 (77.3)	
Education (%):				
Up to primary	95 (30.2)	13 (19.4)	82 (33.2)	0.14
Secondary	157 (50)	33 (49.3)	124 (50.2)	
Some university	61 (19.4)	21 (31.3)	40 (16.2)	
Active smokers (%)	82 (26.1)	49 (73.1)	180 (72.9)	0.66
Pack-years	47.7 (31.1)	42.7 (23.2)	49.7 (34.1)	0.08
BMI (Kg/m^2)	26.4 (5.3)	25.3 (4.9)	26.7 (5.4)	0.09
Chronic bronchitis (%)	162 (61.3)	27 (48.2)	135 (73.5)	0.023
Emphysema (%)	198 (75)	45 (80.3)	153 (73.5)	0.29
ACO (%)	30 (9.6)	8 (11.9)	22 (8.9)	0.46
Bronchiectasis (%)	40 (12.8)	11 (16.6)	29 (11.8)	0.29
Charlson index	4.2 (1.6)	3.9 (1.7)	4.3 (1.6)	0.049
mMRC	1.62 (1)	0.85 (0.3)	1.83 (1)	<0.001
FVC, mL	2880 (892)	3189 (953)	2780 (860)	0.002
FVC (%)	67.5 (14.5)	71.6 (16.1)	65.8 (14.1)	0.019
FEV1, mL	1489 (582)	1758 (633)	1416 (546)	<0.001
FEV1 (%)	52.6 (18)	58.3 (18.3)	51 (17.7)	0.003
Exacerbations in the previous year	1.27 (2.7)	0.54 (1.2)	1.47 (3)	0.004
BODEx index	2.3 (1.8)	1.3 (1.2)	2.6 (1.8)	<0.001
CAT score	14.3 (8.7)	12.2 (7.6)	14.8 (8.9)	0.043
CCQ score	2.03 (1.3)	1.77 (1.3)	2.1 (1.3)	0.033
Minutes walked/day	82.2 (76.6)	117.7 (56)	72.3 (78.7)	<0.001

Footnote: Values are mean (SD, except otherwise indicated. BMI: Body mass index; ACO: Asthma-COPD overlap; mMRC: modified Medical Research Council; CAT: COPD assessment test; CCQ: clinical COPD questionnaire; FVC: Forced vital capacity; FEV1: Forced expiratory volume in 1 second.

Table 3. Pharmacologic treatment for COPD of controlled and uncontrolled patients

	All (n=314)	**Controlled (n=67)**	**Uncontrolled (n=247)**	**P value**
SABA	55.9	43.6	59.1	0.04
SAMA	22.8	10.9	25.9	0.018
LABA	73.1	63.6	75.6	0.052
LAMA	71.4	72.7	71.1	0.80
ICS	38.8	25.7	42.2	0.014
Theophylline	6	0	7.7	0.020
Roflumilast	3.8	5.4	3.3	0.47
Macrolides	1.1	0	1.4	0.37
LTOT	6.7	3	7.7	0.17
Influenza vaccine	52.1	36.3	56.2	0.009
Antipneumococcal vaccine	36.5	20	40.9	0.004
Treatment patterns				
SAMA/SABA alone or in combination	1.1	1.8	1	0.60
LABA alone	10.5	12.4	10.2	0.66
LAMA alone	18.3	25.8	16.3	0.07
ICS alone	0.6	0	0.8	0.46
LABA/LAMA	26.3	28.8	25.6	0.60
ICS/LABA	11.2	7.6	12.2	0.29
ICS/LAMA	1.9	3	1.6	0.46
ICS/LABA/LAMA	25	15.2	27.6	0.037

Footnote: Values in percentages, %. SABA: short-acting beta-2 agonists; SAMA: Short-acting antimuscarinic agents; LABA: Long-acting beta-2 agonists; LAMA: Long-acting antimuscarinic agents; ICS: Inhaled corticosteroids; LTOT: Long-term oxygen therapy.

Table 4. Factors accounting for the uncontrolled status (high impact or instability) of the COPD patients by level of severity.

	Patients with high impact or instability due to:		**All (n=314)**
	Mild/moderate (n=276)	**Severe (n=39)**	
Impact variables			
Dyspnea (mMRC)	101 (36.7)	33 (84.6)	134 (42.6)
Rescue medication	60 (21.7)	14 (35.9)	74 (23.5)
Physical activity	86 (31.1)	12 (30.7)	98 (31.2)
Sputum	42 (15.2)	10 (25.6)	52 (16.6)
Any clinical criteria	173 (62.7)	38 (97.4)	211 (67.2)
CAT score	165 (59.8)	23 (58.9)	188 (59.8)
CCQ score	189 (68.5)	29 (74.3)	218 (66.5)
Stability variables			
Exacerbations	49 (17.7)	20 (51.2)	69 (21.9)
Changes in CAT	87 (31.7)	15 (38.4)	102 (32.6)
Changes in CCQ	127 (46.3)	19 (48.7)	146 (46.6)
Any exacerbations or changes in CAT	116 (42.2)	26 (66.6)	142 (45.2)
Uncontrolled	208 (75.6)	39 (100)	247 (78.6)

Footnote: Values are n (%). Percentages calculated on non-missing data.

CAT indicates COPD assessment test; CCQ, clinical COPD questionnaire; mMRC modified Medical Research Council.

Table 5. Backward logistic multivariate model to control.

	Unadjusted OR (CI95%)	**P value**	**Adjusted OR (CI95%)**	**P value**
Age, years	0.99 (0.96-0.02)	0.53		
Sex (male)	3.87 (1.68-8.86)	0.001	3.57 (1.16-10.92)	0.019
Living alone	0.52 (0.23-1.16)	0.09		
Higher academic education	2.24 (1.09-4.59)	0.02		
BMI, Kg/m2	0.94 (0.90-1.002)	0.057		
Charlson index	0.85 (0.69-0.95)	0.049		
Chronic bronchitis	0.50 (0.27-0.91)	0.024	0.55 (0.29-0.93)	0.04
Previous exacerbations	0.41 (0.22-0.77)	0.005	0.45 (0.22-0.91)	0.049

Footnote: OR: odds ratio; CI: Confidence interval; BMI: Body mass index

Table 6. Evaluation of low impact, stability and control of COPD by using different criteria, either clinical, CAT or CCQ questionnaires.

	Impact: clinical[1] **Stability:** EX	**Impact:** CAT **Stability:** CAT	**Impact:** CCQ **Stability:** CCQ	**Impact:** clinical[1] **Stability:** EX & CAT	**Impact:** CAT **Stability:** EX & CAT	**Impact:** clinical[1] & CAT **Stability:** EX & CAT	**Impact:** clinical[1] & CCQ **Stability:** EX & CCQ
BODEx ≤4 versus ≥5							
Low Clinical Impact	104 (33)	127 (40)	91 (29)	104 (33)	127 (40)	55 (18)	44 (14)
Stable	246 (78)	211 (67)	215 (70)	172 (55)	172 (55)	172 (55)	177 (57)
Control of COPD	99 (32)	101 (32)	83 (27)	67 (21)	89 (28)	42 (13)	40 (13)
BODEx ≤2 versus ≥3							
Low Clinical impact	126 (40)	171 (54)	129 (42)	126 (40)	171 (54)	82 (26)	63 (20)
Stable	246 (78)	172 (55)	215 (70)	172 (55)	172 (55)	172 (55)	177 (57)
Control of COPD	117 (37)	117 (37)	113 (37)	83 (27)	117 (37)	62 (20)	53 (17)

Footnote: Values are n (%). Percentages calculated on non-missing data.

CAT indicates COPD assessment test; CCQ, clinical COPD questionnaire; EX, exacerbations; COPD, chronic obstructive pulmonary disease; BODEx: Body mass index, Obstruction, Dyspnea and Exacerbations index.

[1] Clinical impact is defined using dyspnea (mMRC), rescue medication, daily physical activity and sputum color.