COPD clinical control as a predictor of future exacerbations: concept validation in the SPARK study population

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ABSTRACT

The concept of chronic obstructive pulmonary disease (COPD) control has been proposed to guide treatment decisions in COPD. In this study, we aimed to validate the prospective value of this concept in the SPARK study population. Control was assessed based on COPD stability and impact. Patients with low impact and stability during weeks 1–12 were classified as controlled, and exacerbations were measured during a 52-week follow-up. Of the 2044 patients included a majority were non-controlled (80%), frequently due to high impact. During the follow-up, the rate of moderate/severe exacerbations was significantly lower in controlled patients (rate ratio, 0.56, 95% CI 0.48 to 0.65 p<0.0001) and time-to-first moderate/severe exacerbation was significantly delayed. This study demonstrated an association between control status and risk of exacerbations.

INTRODUCTION

Current recommendations for treatment of chronic obstructive pulmonary disease (COPD) are based on exacerbations, symptoms or clinical phenotypes.[1–3] However, in the same severity group or phenotype, a patient may experience variation in symptoms, more frequent exacerbations or an impairment in health status that does not result in a change in category, and therefore, no step-up or step-down recommendation is established.

The concept of disease control has been well characterised in asthma. Physicians dispose of several evaluation tools, such as the Asthma Control Questionnaire, which allow to determine the level of control and subsequently to guide therapy in clinical practice.[4] Recently, José Soler-Cataluña *et al*[5 6] proposed a definition to assess the concept of control in COPD based on impact of the disease and clinical stability. Impact is related to the manifestations of the disease and it is assessed by symptoms reported by the patient, or using a symptom questionnaire.[7 8] Two previous studies have partially addressed the validation of control in COPD.[9 10] However, prospective, follow-up studies are required to investigate the prognostic value of the concept of control.

In the present analysis, we aimed to assess the association of the proposed concept of COPD control on future exacerbations in a population of severe and very severe patients with COPD from the SPARK study population.[11]

METHOD

The SPARK study was a 64-week, double-blind, parallel-group multicentre study, which included patients with severe and very severe COPD between April 2010 and July 2012, with at least one moderate exacerbation the previous 12 months.[11] Patients were randomised to receive tiotropium 18 µg, glycopyrronium 50 µg or a fixed-dose combination of indacaterol 110 µg and glycopyrronium 50 µg for 64 weeks.

In this post hoc analysis, we investigated the association of control status on future exacerbations. Control was defined based on impact and stability. The study was divided into two time periods: weeks 1–12 were used to assess control status, and a follow-up period of 52 weeks (weeks 13–64) to evaluate the predictive value of control (online supplementary figure 1).

'Low impact' or 'high impact' was defined based on the assessment of dyspnoea and sputum colour from the electronic diary and use of rescue medication from the electronic case report form at the end of week 12. Patients were classified as high impact if they had any of dyspnoea ≥2, sputum colour 2–3 (yellow or green) or >2 puffs/day rescue medication use or as low impact if they did not fulfil any of the previous. Alternatively, impact could be assessed using the Saint George's Respiratory Questionnaire (SGRQ) score (see online supplemental material and supplementary figure 3). Stability was defined as the absence of exacerbations during 12 weeks. Patients with low impact and no exacerbations during weeks 1–12 were classified as controlled and patients with high impact and/or an exacerbation during this period were classified as non-controlled. For the validation of the concept of control, rate of moderate/severe and all exacerbations; and time-to-first moderate/severe and all exacerbation were assessed during a follow-up. The statistical analysis is described in the online supplemental material

RESULTS

A total of 2044 patients were included. At week 12, only 418 (20%) of patients were classified as controlled. Of the non-controlled patients, 1539 (95%) had high impact of COPD, being the major contributors dyspnoea (72.5%), sputum colour (22%) and use of rescue medication (75.6%). Overall, most patients (76%) were stable having no moderate/severe exacerbations during weeks 1–12. Among those classified as non-controlled, 25%

Table 1 Demographic and clinical characteristics of patients based on control status

Characteristic	Control assessed using e-diary/eCRF (n=2044)		
	Controlled (n=418)	Non-controlled (n=1626)	P value
Age, years	62.8±8.4	63.3±7.8	0.2497
Men, n (%)	309 (73.9)	1227 (75.5)	0.5164
BMI, kg/m^2	25.1±5.4	25.4±5.5	0.3806
Current smoker, n (%)	150 (35.9)	627 (38.6)	0.3148
Duration of COPD, years	6.3±5.4	7.3±5.5	0.0007
COPD severity, n (%)			
Severe	361 (86.4)	1268 (78.0)	0.0003
Very severe	56 (13.4)	357 (22.0)	
ICS users at baseline, n (%)	280 (67.0)	1259 (77.4)	<0.0001
COPD exacerbations, n (%)			
1	350 (83.7)	1226 (75.4)	0.0013
≥2	63 (15.1)	378 (23.2)	
Baseline COPD symptom score*	5.2±2.7	7.7±2.9	<0.0001
SGRQ total score	32.8±15.1	49.3±17.6	<0.0001
Postbronchodilator FEV_1, % predicted	39.1±7.7	36.9±8.1	<0.0001
Postbronchodilator FEV_1, mL	1100±300	1000±290	<0.0001
Postbronchodilator FEV_1/FVC, %	41.7±9.9	38.8±9.2	<0.0001

Data are presented as mean (SD) unless otherwise mentioned.
*COPD symptom score based on dyspnoea, sputum colour and use of rescue medication (see online supplementary material 2).
BMI, body mass index; COPD, chronic obstructive pulmonary disease; eCRF, electronic case report form; e-diary, electronic patient diary; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroids; SGRQ, St. George's Respiratory Questionnaire.

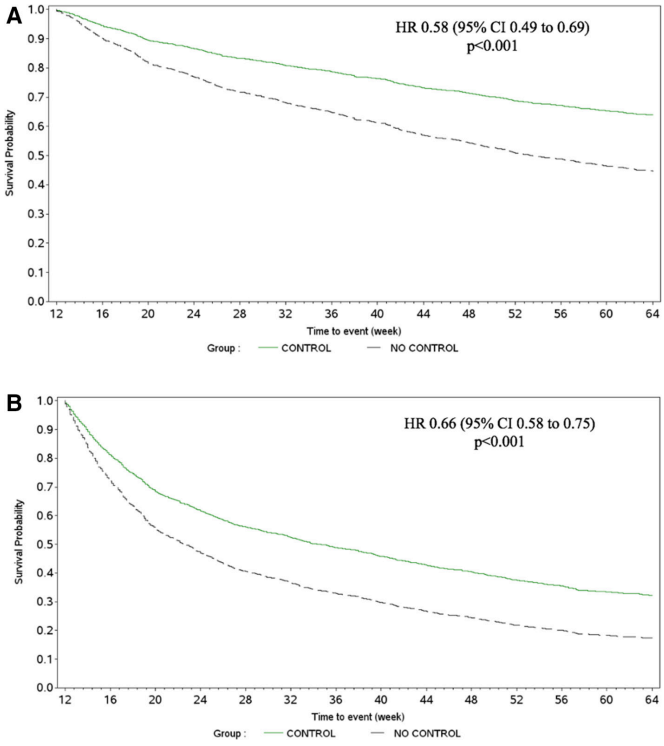

Figure 1 Kaplan-Meier plot of time-to-first (A) moderate/severe exacerbation and (B) all (mild, moderate and severe) exacerbation in controlled and non-controlled patients during 52 weeks† adjusted by prior exacerbations and treatment. †Control status was based on clinical variables in the e-diary/eCRF. eCRF, electronic case report form; e-diary, electronic diary.

fulfilled both high impact and instability (see online supplementary figure 2).

Controlled patients had a slightly better lung function with less patients classified as very severe, were less frequently frequent exacerbators and less patients were treated with inhaled corticosteroids (ICS) at baseline. They also had significantly better health-related quality of life measured by the SGRQ and a lower COPD symptom score (table 1).

Control status and exacerbation events

The rate of moderate/severe exacerbation events was significantly lower in the controlled group (annualised rate in controlled patients 0.54, 95% CI 0.43 to 0.69; annualised rate in non-controlled patients 0.98, 95% CI 0.81 to 1.18; rate ratio (RR), 0.56, 95% CI 0.48 to 0.65 p<0.0001). Time-to-first moderate/severe exacerbation was also significantly delayed in the controlled group (93 days (95% CI 84 to 102) for controlled, 222 days (95% CI 184 to 222) for non-controlled; HR (HR), 0.58, 95% CI 0.49 to 0.69 p<0.0001); because less than 50% of patients in the controlled group had an exacerbation, the time by which at least 25% of patients had a first to moderate/severe exacerbation was calculated instead of the median time. Similar trends were observed for all exacerbations with significantly lower rate (RR 0.71, 95% CI 0.63 to 0.80, p<0.0001) and delayed time-to-first exacerbation in the controlled versus the non-controlled group (172 (95% CI 114 to 219) vs 75 (95% CI 65 to 83) days, HR, 0.66, 95% CI 0.58 to 0.75 p<0.0001) (figure 1) (Adjusted by prior history of exacerbations and treatment, see online supplementary material for statistical analysis).

DISCUSSION

Our results showed that a low number of patients could be classified as 'controlled' using impact and stability with the proposed thresholds as indicators of control status. Among the different criteria proposed, having a high impact of the disease was the most frequent cause for being classified as non-controlled. Time-to-first exacerbation was found to be significantly delayed and exacerbation rate was lower in patients who were classified as controlled, therefore, indicating that evaluation of control status has prognostic implications.

We have evaluated the prognostic value of the concept of control previously developed by Soler-Cataluña *et al*.[6] This concept was proposed to monitor the state of the disease in patients with COPD, and thus to help in optimising pharmacological and non-pharmacological treatment in daily clinical practice. The applicability of control has already been assessed in cross-sectional and database studies. Nibber *et al*[9] aimed to validate the definition of control in the OPCRD. The authors used the proposed definition to retrospectively assess the status of control during a period of 3 months, followed by a 12-month follow-up. In this cohort, 90% of patients had mild-to-moderate COPD and within this group only 4.5% of patients were defined as controlled, while no severe-to-very severe patients were identified as controlled. Time-to-first exacerbation was longer for the controlled patients with mild-to-moderate COPD, therefore, demonstrating the association between control status and exacerbations.

More recently, a cross-sectional analysis of control status from an international, prospective study of a cohort of 314 patients with COPD has been reported.[10] In this cohort, up to 21% of

the individuals were classified as controlled, all having mild-to-moderate disease. Two-thirds of the patients did not fulfil control criteria due to the high impact of the disease, being high dyspnoea score and low physical activity the most common reasons. The results of both studies reflected that the criteria or thresholds selected to define control were too restrictive. The number of severe/very severe patients was low in both studies and none of them was considered controlled based on the criteria used. Besides, the study design did not allow validating the concept of control as predictor of future outcomes.

In accordance with the previous studies, we observed that the majority of COPD individuals in the SPARK population did not fulfil the criteria for control, and most of them were classified as non-controlled due to high impact of the disease. The rate of exacerbations was lower in the controlled group during 1-year follow-up. Time-to-first exacerbation was also significantly delayed (for all exacerbations and for moderate/severe exacerbations) in patients who were controlled.

We observed that controlled patients, although less frequently, still presented exacerbations during follow-up. In COPD, it may be difficult to reach absolute control with the current therapies, and there is not a defined intermediate stage level of control.[12]

This study has some limitations that need to be acknowledged. The design of the study limited inclusion and assessment only to patients with severe and very severe COPD, and therefore, these results cannot be extrapolated to less severe patients with COPD. Validation of these findings in a prospective study including a broader spectrum of COPD patients would help to support the thresholds evaluated here and serve as additional proof for the predictive utility of control status. Despite these limitations, the large study sample size and the availability of high-quality data from 1-year follow-up support the suitability of the SPARK study population to test the concept of control.

In conclusion, these findings support the utility of the concept of clinical control as a predictor of future risk of exacerbations and, moreover, as a tool to guide treatment intensity in patients with COPD. Future prospective studies may confirm this prognostic value in populations of less severe COPD.

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Contributors MB, KK, KM, BA, JJJJS-C, MM and JAW contributed to study design. KK, KM, SS and JAW were responsible for planning and conducting the study. SS, KK, KM,MM and JAW performed and/or supervised data analysis. MB was responsiblefor drafting the manuscript. All authors contributed to data interpretationand to development of the final manuscript. MM and JAW take responsibilityfor the integrity of the data and the accuracy of the data analysis.

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Competing interests MB has received speaker fees from Menarini, GlaxoSmithKline, Gebro Pharma, Boehringer Ingelheim, CSL Behring and Grifols and consulting fees from Novartis. KK is an employee and shareholder of Novartis Pharma AG, Basel, Switzerland. KM is an employee of Novartis Pharma AG, Basel, Switzerland. SS is an employee and shareholder of Novartis Pharmaceuticals, New Jersey, USA. BA reports personal fees and grants from Novartis AG, personal fees from Boehringer Ingelheim, personal fees from GSK, personal fees from AstraZeneca, grants and personal fees from Menarini, outside the submitted work. JJJJS-C has received speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Esteve, Ferrer, GSK, Menarini, Novartis, and Pfizer, and consulting fees from AirLiquide, Boehringer Ingelheim, Chiesi, GSK, AstraZeneca, Ferrer and Novartis. MM has received speaker fees from Astra Zeneca, Boehringer Ingelheim, Chiesi, Cipla, Menarini, Rovi, Bial, Grifols and Novartis, consulting fees from Astra Zeneca, Ferrer, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Bial, Gebro Pharma, CSL Behring, Laboratorios Esteve, Mereo Biopharma, Verona Pharma, pH Pharma, Novartis and Grifols and research grants from GlaxoSmithKline and Grifols, outside the submitted work. JAW reports grants from GSK, Johnson and Johnson, Novartis, Boehringer Ingelheim, Astra Zeneca, outside the submitted work.

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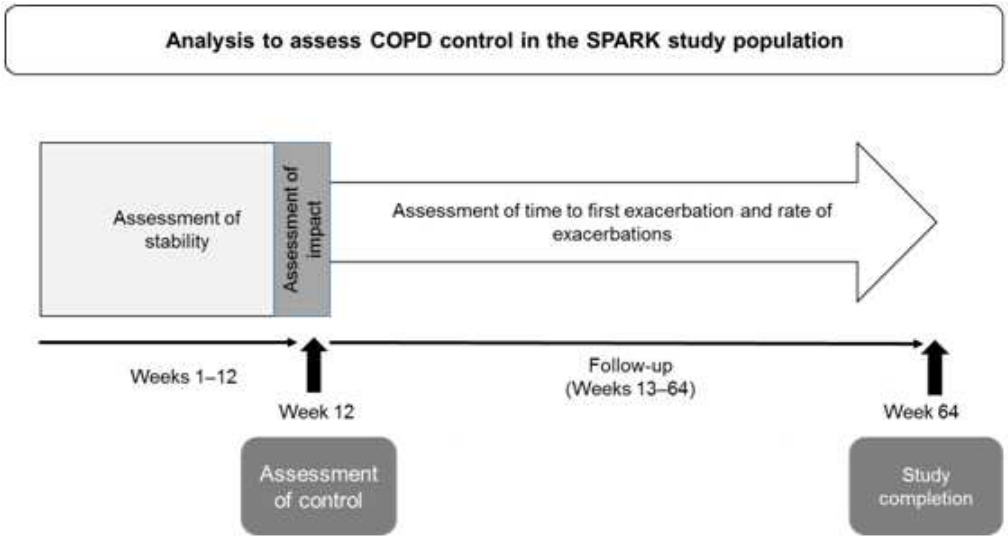
Analysis to assess COPD control in the SPARK study population
Assessment of stability
Assessment of impact
Assessment of time to first exacerbation and rate of exacerbations
Weeks 1–12
Week 12
Follow-up (Weeks 13–64)
Week 64
Assessment of control
Study completion

Online Supplemental material for the manuscript: “COPD clinical control as a predictor of future exacerbations: concept validation in the SPARK study population”

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METHODS

Spark Study population

Patients with COPD aged ≥40 years with severe-to-very severe airflow limitation, defined by a post-bronchodilator forced expiratory volume in 1 second (FEV_1) <50% predicted and FEV_1/forced vital capacity (FVC) <0.70, current or previous smokers with a smoking history ≥10 pack-years, were included in the analysis.

Definition of control

In the present analysis, patients were classified as “Low-impact” or “High-impact” based on the assessment of dyspnoea[1] and sputum colour[2] from the electronic diary (e-diary) and use of rescue medication[3] from the electronic case report form (eCRF). Dyspnoea was calculated as the average of the morning score in the 7 days prior to Week 12, assessed on a scale of 0–3 based on the patient’s response in the e-

Barrecheguren M, *et al*. *Thorax* 2020;0:1–3. doi: 10.1136/thoraxjnl-2018-212752

diary to the question: “During what activities did you first feel breathless in the last 12 hours?”, with 0 = never / only when running, 1 = when walking uphill or upstairs, 2 = when walking on flat ground, and 3 = at rest. Sputum colour was assessed similarly based on the patient’s response to: “What colour was the sputum you produced during the past 12 hours?”, with 0 = none, 1 = white-grey, 2 = yellow, and 3 = green. Rescue medication was assessed as an average of the 7 days prior to Week 12 and represents the number of puffs taken per day. patients were classified as high-impact if they had any of dyspnoea ≥2, sputum colour 2–3 (yellow or green) or >2 puffs/day rescue medication use, or as low-impact if they didn´t fulfil any of the previous. Alternatively, impact could be assessed using the Saint George’s Respiratory Questionnaire (SGRQ) score[4]. In this classification, patients with SGRQ score <50 were categorized as low-impact and SGRQ ≥50 as high-impact. This cut-off was considered equivalent to the CAT cut-off of 20 in the previous definition[5].

Stability was defined as the absence of exacerbations during 12 weeks. A COPD exacerbation was defined in terms of requirement for treatment with systemic corticosteroids or antibiotics or both, or hospitalization due to increase in respiratory symptoms, including an emergency room visit for >24 hours. (Supplementary figure 1)

Statistical analysis

Demographic and clinical characteristics of patients controlled and non-controlled were compared. Summary statistics, including mean, standard deviation and median, or numbers and proportions of patients, were calculated for the patient demographics and study baseline characteristics by controlled and non-controlled groups. The two-sample *t*-test for continuous variables and the Chi-square test for categorical ones were used to evaluate the differences between controlled and non-controlled groups. The number of moderate/severe, and all exacerbations were summarized using descriptive statistics and were analysed using a generalized linear model assuming the negative binomial distribution with control and prior history of exacerbations as fixed-effect factors. The log exposure in years (duration of the study) was included as an offset

Barrecheguren M, *et al*. *Thorax* 2020;0:1–3. doi: 10.1136/thoraxjnl-2018-212752

variable in the model. Time-to-first exacerbation was analysed using the Cox proportional hazard model with the same above terms and estimates of time to event were obtained using the Kaplan-Meier estimation method. The analysis was adjusted for treatment arm. Statistical significance was defined as two-sided p<0.05. All the analyses were performed using Statistical Analysis Software (SAS) version 9.3.

Ethics

Approvals from institutional review boards or ethic committees were obtained from each investigator site. The SPARK study is registered with ClinicalTrials.gov (NCT01120691).

RESULTS

Control status assessed using SGRQ

When using SGRQ for impact assessment, 48% of patients were classified as having their COPD controlled (n=976). More patients had low impact than high impact (59% *versus* 41%). The distribution of patients based on fulfilment of criteria for impact based on SGRQ scores and stability is presented in supplementary figure 2.

Controlled patients, compared to non-controlled patients, had a significantly shorter duration of COPD (6.8 *versus* 7.4 years, p<0.05), were less severe (14.1% *versus* 25.8% very severe patients, p<0.0001), fewer were frequent exacerbators (17.1% *versus* 25.9%, p<0.0001), had a lower COPD symptom score (6.0 *versus* 8.2 points, p<0.0001), while lung function was similar between groups (post-bronchodilator FEV_1 % predicted 38.6% *versus* 36.1%, p<0.0001) (table 1).

Based on the SGRQ definition of control status, the rate of moderate/severe exacerbation was significantly lower in the controlled group (RR 0.59, 95% CI 0.53–0.66 p<0.0001). Time-to-first moderate/severe exacerbation was also significantly delayed in the controlled group (181 days (95% CI 151-205) vs 74 days (95%CI 57-88) for controlled vs no controlled; HR 0.59, 95% CI 0.52–0.68 p<0.0001) (table 2) (supplementary figure 3) because less than 50% of patients in the controlled group had an exacerbation, the time by which at least 25% of patients had a first to

Barrecheguren M, *et al*. *Thorax* 2020;0:1–3. doi: 10.1136/thoraxjnl-2018-212752

moderate/severe exacerbation was calculated instead of the median time. Similar trends were observed for all exacerbations with significantly lower rate (RR 0.75, 95% CI 0.68–0.82 p<0.0001) and delayed time-to-first exacerbation in the controlled group *versus* the non-controlled group (119 (95% CI 99-140) *versus* 59 (95% CI 53-70) days, HR 0.72, 95% CI 0.65–0.79 p<0.0001)

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Supplementary Tables

Supplementary Table 1. Demographic and clinical characteristics of patients based on control status

	Control assessed using e-diary/eCRF (N=2044)		**Control assessed using SGRQ (N=2029)**	
Characteristic	**Controlled**	**Non-controlled**	**Controlled**	**Non-controlled**

	(n=418)	**(n=1626)**	**(n=976)**	**(n=1053)**
Age, years	62.8 ± 8.4	63.3 ± 7.8	63.7 ± 8.0**	62.7 ± 7.8
Men, n (%)	309 (73.9)	1227 (75.5)	741 (75.9)	783 (74.4)
BMI, kg/m^2	25.1 ± 5.4	25.4 ± 5.5	25.2 ± 5.2	25.4 ± 5.7
Current smoker, n (%)	150 (35.9)	627 (38.6)	358 (36.7)	415 (39.4)
Duration of COPD, years	6.3 ± 5.4**	7.3 ± 5.5	6.8 ± 5.5*	7.4 ± 5.5
COPD severity, n (%)				
Severe	361 (86.4)**	1268 (78.0)	837 (85.8)***	780 (74.1)
Very severe	56 (13.4)	357 (22.0)	138 (14.1)	272 (25.8)
ICS users at baseline, n (%)	280 (67.0)***	1259 (77.4)	694 (71.1)***	837 (79.5)
COPD exacerbations, n (%)				
1	350 (83.7)**	1226 (75.4)	790 (80.9)***	772 (73.3)
≥2	63 (15.1)	378 (23.2)	167 (17.1)	273 (25.9)
Baseline COPD symptom score	5.2 ± 2.7***	7.7 ± 2.9	6.0 ± 2.8***	8.2 ± 2.8
SGRQ total score	32.8 ± 15.1***	49.3 ± 17.6	33.0 ± 11.0***	58.0 ± 15.4
Post-bronchodilator FEV_1, % predicted	39.1 ± 7.7***	36.9 ± 8.1	38.6 ± 7.6***	36.1 ± 8.3
Post-bronchodilator FEV_1, mL	1100 ± 300***	1000 ± 290	1100 ± 290***	1000 ± 300
Post-bronchodilator FEV_1/FVC, %	41.7 ± 9.9***	38.8 ± 9.2	40.2 ± 9.4**	38.7 ± 9.4

Data are presented as mean (SD) unless otherwise mentioned. *p<0.05; **p<0.001; ***p<0.0001.

BMI: body mass index; COPD: chronic obstructive pulmonary disease; eCRF: electronic case report form; e-diary: electronic diary; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; ICS: inhaled corticosteroid; SGRQ: St. George's Respiratory Questionnaire.

Supplementary Table 2. Rate and risk of COPD exacerbations† during the 52-week follow-up in the SPARK study population

Characteristic	Control assessed using e-diary/eCRF (N=2044)		Control assessed using SGRQ (N=2029)	
	Controlled	Non-controlled	Controlled	Non-controlled
Annualized rate of moderate/severe exacerbations	0.54 (0.43–0.69)	0.98 (0.81–1.18)	0.68 (0.55–0.83)	1.15 (0.94–1.39)
Rate ratio (95% CI)	0.56 (0.48–0.65)***		0.59 (0.53–0.66)***	
Hazard ratio (95% CI)‡	0.58 (0.49–0.69)***		0.59 (0.52–0.68)***	
Annualized rate of all (mild, moderate and severe) exacerbations	2.58 (2.17–3.06)	3.80 (3.10–4.67)	2.97 (2.57–3.43)	3.98 (3.45–4.60)
Rate ratio (95% CI)	0.71 (0.63–0.80)***		0.75 (0.68–0.82)***	
Hazard ratio (95% CI)†	0.66 (0.58–0.75)***		0.72 (0.65–0.79)***	

†Estimates and CIs of quartiles are obtained from the Kaplan-Meier estimation method; ‡hazard ratio represents the risk for the

time-to-first exacerbation and was estimated using the Cox proportional hazard model.***p<0.0001.

CI: confidence interval; COPD: chronic obstructive pulmonary disease; eCRF: electronic case report form; e-diary: electronic diary; SGRQ: St. George's Respiratory Questionnaire.

Supplementary Figure 1: **Analysis design**

Footnote: Stability was determined by the occurrence of moderate/severe exacerbations, and was assessed during Weeks 1–12. Impact was classified at Week 12, based on either of two alternative assessments: (a) dyspnoea (score: 2 or ≥2), sputum colour (absent/white or dark), and rescue medication use (≤2 or >2 times per day) [e-diary/eCRF]; or (b) SGRQ score <50 or ≥50. Control was assessed based upon impact and stability. eCRF: electronic case report form; e-diary: electronic diary; SGRQ: St. George's Respiratory Questionnaire.

Supplementary Figure 2:

Distribution of patients based on fulfilment of criteria for control based on e-Diary/eCRF

Barrecheguren M, *et al. Thorax* 2020;0:1–3. doi: 10.1136/thoraxjnl-2018-212752

and SGRQ

Footnote: eCRF: electronic case report form; e-diary: electronic diary, SGRQ: St. George's Respiratory Questionnaire.

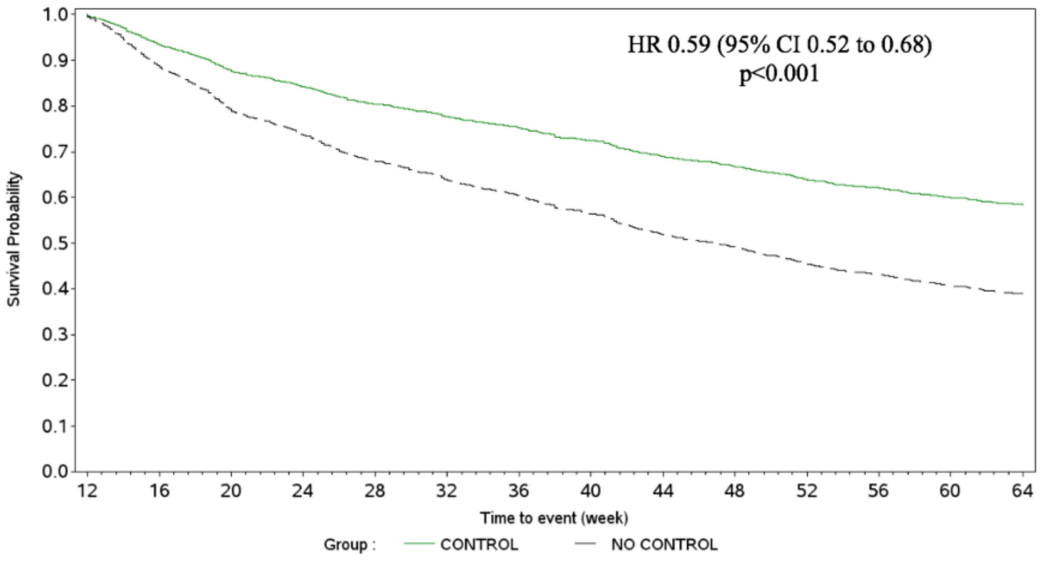
Supplementary Figure 3: **Kaplan-Meier plot of time-to-first (a) moderate/severe exacerbation and (b) all (mild, moderate and severe) exacerbation in controlled and non-controlled patients during 52 weeks† adjusted by prior exacerbations and treatment arm**

Barrecheguren M, *et al. Thorax* 2020;0:1–3. doi: 10.1136/thoraxjnl-2018-212752

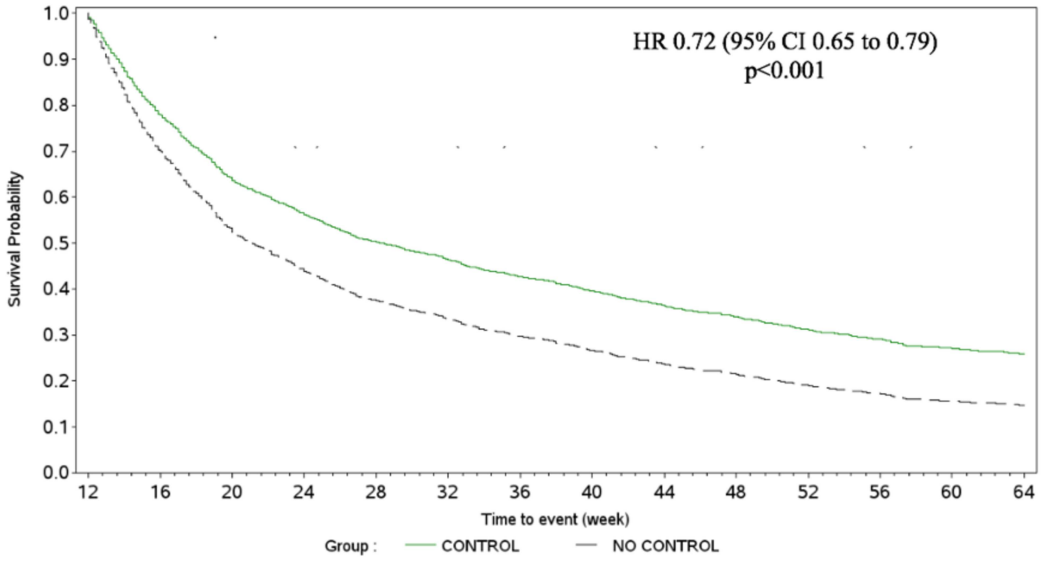
Footnote: †Control status was based on SGRQ. HR: hazard ratio; SGRQ: St. George's Respiratory Questionnaire

Barrecheguren M, *et al. Thorax* 2020;0:1–3. doi: 10.1136/thoraxjnl-2018-212752

a)


HR 0.59 (95% CI 0.52 to 0.68)
p<0.001
Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
12 16 20 24 28 32 36 40 44 48 52 56 60 64
Time to event (week)
Group : CONTROL NO CONTROL

b)


HR 0.72 (95% CI 0.65 to 0.79)
p<0.001
Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
12 16 20 24 28 32 36 40 44 48 52 56 60 64
Time to event (week)
Group : CONTROL NO CONTROL

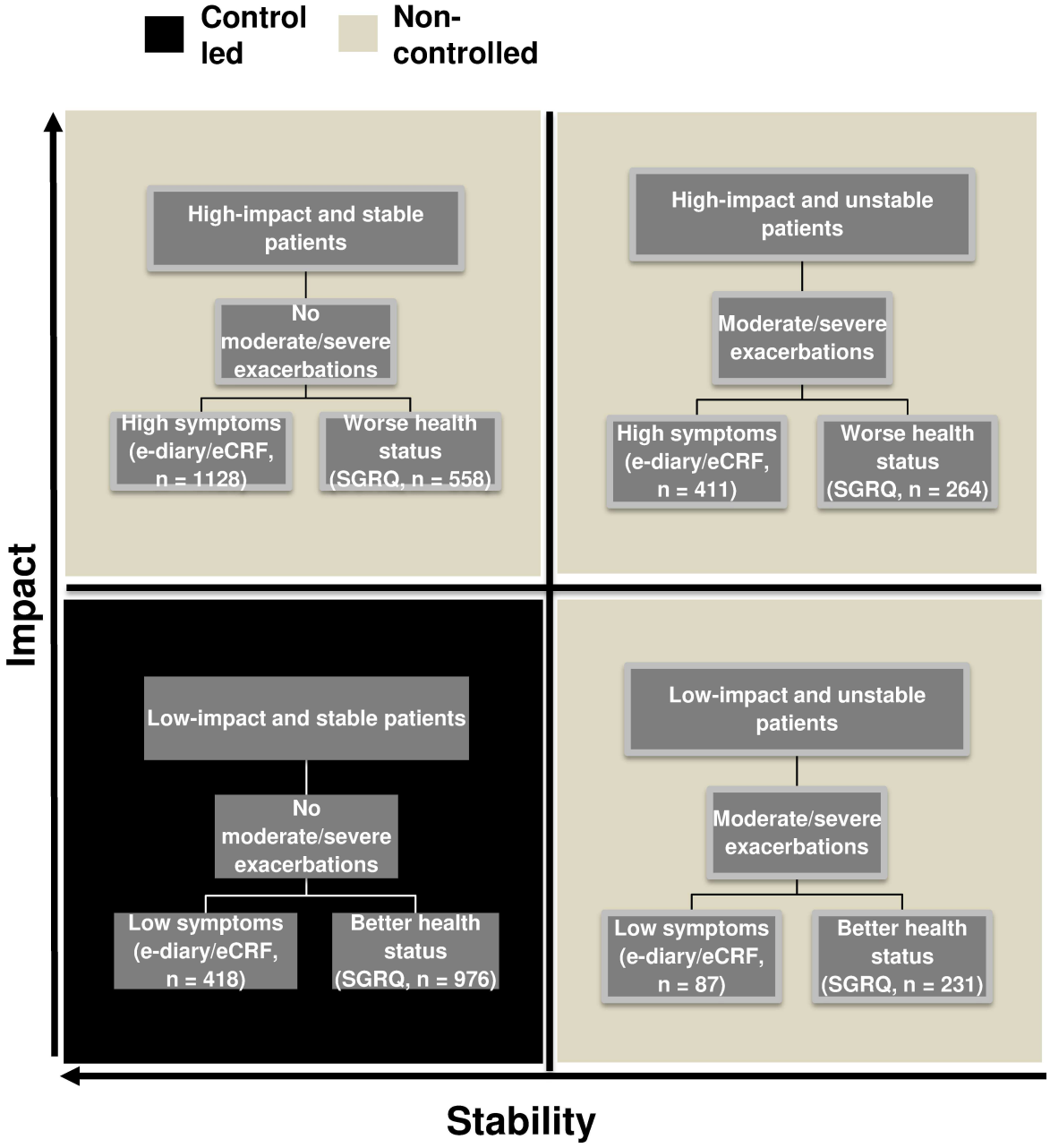

Control led
Non-controlled
High-impact and stable patients
No moderate/severe exacerbations
High symptoms (e-diary/eCRF, n = 1128)
Worse health status (SGRQ, n = 558)
High-impact and unstable patients
Moderate/severe exacerbations
High symptoms (e-diary/eCRF, n = 411)
Worse health status (SGRQ, n = 264)
Low-impact and stable patients
No moderate/severe exacerbations
Low symptoms (e-diary/eCRF, n = 418)
Better health status (SGRQ, n = 976)
Low-impact and unstable patients
Moderate/severe exacerbations
Low symptoms (e-diary/eCRF, n = 87)
Better health status (SGRQ, n = 231)
Impact
Stability

Figure 3