The Relationship Between 24-Hour Symptoms and COPD Exacerbations and Healthcare Resource Use: Results from an Observational Study (ASSESS)

Marc Miravitlles\textsuperscript{a}, Heinrich Worth\textsuperscript{b}, Juan José Soler-Cataluña\textsuperscript{c}, David Price\textsuperscript{d}, Fernando De Benedetto\textsuperscript{e}, Nicolas Roche\textsuperscript{f}, Nina S. Godtfredsen\textsuperscript{g}, Thys van der Molen\textsuperscript{h}, Claes-Göran Löfdahl\textsuperscript{i}, Laura Padullés\textsuperscript{j}, and Anna Ribera\textsuperscript{k}

\textsuperscript{a}Pneumology Department, Hospital Universitari Vall d’Hebron, Ciber de Enfermedades Respiratorias (CIBERES), Barcelona, Spain; \textsuperscript{b}Fachartzforum Fürth, Fürth, Germany; \textsuperscript{c}Servicio de Neumología, Hospital Arnuad de Vilanova, Valencia, Spain; \textsuperscript{d}Centre of Academic Primary Care, University of Aberdeen, Aberdeen, UK; \textsuperscript{e}Specialization School in Internal Medicine, G. D’Annunzio, University of Chieti, Chieti, Italy; \textsuperscript{f}Cochin Hospital, AP-HP, Paris Descartes University (EA2511), Paris, France; \textsuperscript{g}Department of Respiratory Medicine, Hvidovre University Hospital, Hvidovre, Denmark; \textsuperscript{h}Department of Primary Care, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; \textsuperscript{i}Department of Respiratory Medicine and Allergology, Lund University Hospital, Lund, Sweden; \textsuperscript{j}Medical Affairs, Almirall S.A., Barcelona, Spain; \textsuperscript{k}Medical Affairs, AstraZeneca PLC, Barcelona, Spain

ABSTRACT
This observational study assessed the relationship between nighttime, early-morning and daytime chronic obstructive pulmonary disease (COPD) symptoms and exacerbations and healthcare resource use. COPD symptoms were assessed at baseline in patients with stable COPD using a standardised questionnaire during routine clinical visits. Information was recorded on exacerbations and healthcare resource use during the year before baseline and during a 6-month follow-up period. The main objective of the analysis was to determine the predictive nature of current symptoms for future exacerbations and healthcare resource use. 727 patients were eligible (65.8\% male, mean age: 67.2 years, % predicted forced expiratory volume in 1 second: 52.8\%); 698 patients (96.0\%) provided information after 6 months. Symptoms in any part of the day were associated with a prior history of exacerbations (all \( p < 0.05 \)) and nighttime and early-morning symptoms were associated with the frequency of primary care visits in the year before baseline (both \( p < 0.01 \)). During follow-up, patients with baseline symptoms during any part of the 24-hour day had more exacerbations than patients with no symptoms in each period (all \( p < 0.05 \)); there was also an association between 24-hour symptoms and the frequency of primary care visits (all \( p \leq 0.01 \)). Although there was a significant association between early-morning and daytime symptoms and exacerbations during follow-up (both \( p < 0.01 \)), significance was not maintained when adjusted for potential confounders. Prior exacerbations were most strongly associated with future risk of exacerbation. The results suggest 24-hour COPD symptoms do not independently predict future exacerbation risk.

Introduction

Patients with chronic obstructive pulmonary disease (COPD) experience a range of respiratory symptoms, including breathlessness, cough, sputum production and chest tightness. COPD symptoms generally worsen as the disease progresses, reducing the patient’s quality of life (1). In many patients, symptoms fluctuate from day-to-day and also within the course of the 24-hour day, with the most severe symptoms occurring during the early morning and nighttime (1–3). Morning and daytime symptoms limit the patient’s ability to perform their daily activities, whereas nighttime symptoms reduce sleep quality and may be associated with the long-term effects of sleep deprivation, including cognitive impairment, depression, development or progression of cardiovascular disease, and increased mortality (4–6). International guidelines recommend a comprehensive evaluation of symptoms during the assessment of COPD in routine clinical practice, in order to assess the impact of disease on the patient’s health status. Such assessments are performed using patient questionnaires, such as the COPD Assessment Test (CAT) and COPD Control Questionnaire (7).

Measures of specific symptoms, such as dyspnoea with the modified Medical Research Council (mMRC) questionnaire, may also be employed (7).

Exacerbations are key events in the progression of COPD and are associated with a faster rate of lung function decline (8), impaired health status (8, 9) and increased risk of mortality (10, 11). In addition, they are associated with considerable economic costs (12, 13). As such, reducing the risk of exacerbation is a key goal of COPD therapy. Whilst the contribution of respiratory symptoms to the burden of COPD is now well-established, the relevance of symptoms as prognostic factors and markers of disease severity is unclear. Previous studies have shown an association between both early-morning and nighttime COPD symptoms and a history of more frequent exacerbations (5, 6). The rate and severity of COPD exacerbations have been shown to increase with the severity of airflow limitation, but a prior history of exacerbations is the best predictor of a future moderate or severe exacerbation (14). Other factors shown to be independently associated with an increased exacerbation risk include female gender, poor lung function, poor health status, low level of physical activity, severity of breathlessness, sputum...
and chronic cough, cardiovascular disease as a co-morbidity, anxiety and depression, history of gastro-oesophageal reflux, and increased white blood cell count (15–19). To date, no study has investigated whether symptoms in each part of the 24-hour day are associated with or can be used to predict exacerbation risk.

We have previously reported baseline characteristics and the analysis of primary endpoints from ASSESS, an observational cohort study of patients in clinical practice being treated for COPD, which demonstrated that patients with COPD experience symptoms throughout the whole 24-hour day. In addition, the presence of COPD symptoms in each part of the 24-hour day (nighttime, early morning or daytime) was associated with worse patient-reported outcomes, including more severe breathlessness, worse health status, higher anxiety and depression levels, and worse sleep quality, compared with patients without symptoms during these times (20). Here, we report the results of the analysis of exacerbations in the study population, comprising three parts: a) an investigation of the relationship between baseline nighttime, early-morning and daytime COPD symptoms and exacerbations and healthcare resource use in the year prior to baseline using a pre-planned retrospective analysis; b) confirmation of the findings of the analysis in a pre-planned 6-month prospective follow-up analysis; and c) a post hoc investigation of whether baseline symptoms can be used to predict future risk of exacerbations and healthcare resource use, when potential confounding factors are taken into consideration.

Methods

Study design

This was a multinational, non-interventional, observational study conducted in 85 centres (outpatients and primary care) in eight European countries (20). Patients had a baseline visit (Day 1) and a follow-up telephone interview after 6 months. Information collected on Day 1 included demographics, medical history, current COPD treatments and COPD exacerbations, and healthcare resource use during the previous year. In addition, nighttime, early-morning and daytime COPD symptoms during the previous week were assessed (details given below). During the 6-month follow-up telephone interview, patients provided information on COPD exacerbations and healthcare resource use during the period since baseline. There were no interventions beyond routine clinical care delivered at the discretion of the physician.

The protocol was approved by all necessary ethics committees. All patients provided written informed consent.

Study populations

Detailed inclusion/exclusion criteria have been reported previously (20). Briefly, patients were aged ≥40 years with stable COPD and mild to very severe airflow limitation according to the Global Initiative for chronic Obstructive Lung Disease (GOLD) 2010 spirometric classification (21), were current or former smokers with a smoking history of ≥10 pack-years, and had no history of COPD exacerbation in the previous month.

Exclusion criteria were any change in maintenance COPD treatment in the previous 3 months; a previous diagnosis of asthma, sleep apnoea syndrome or chronic respiratory disease other than COPD; and any acute or chronic condition that would limit the patient’s ability to complete the questionnaires.

Study assessments

COPD symptoms in each part of the 24-hour day were assessed at baseline using a 33-item Nighttime, Morning and Daytime Symptoms of COPD questionnaire, as previously described (20). The questionnaire included questions asking patients about whether they experienced any COPD symptoms (feeling short of breath, coughing, bringing up phlegm or mucus, chest tightness, chest congestion and/or wheezing) during the nighttime, early morning and daytime in the week before baseline. Night-time was defined as the time from when the patient went to bed until the time that they got out of bed to start the day; morning was defined as the time from getting out of bed until approximately 11 am; and daytime was defined as approximately 11 am until the time that the patient went to bed.

COPD exacerbations were assessed based on medical history (year prior to baseline only) and information provided by the patient. A COPD exacerbation was defined as an acute event characterised by a worsening of the patient’s respiratory symptoms that is beyond day-to-day variations and leads to a change in medication. The number of exacerbations overall and the number of exacerbations requiring hospitalisation were assessed. An annual exacerbation rate was calculated based on the total assessment period (i.e. the year before baseline plus the 6-month follow-up period divided by 1.5). Healthcare resource use was assessed by asking patients specific and detailed questions at their first visit about how many times they had visited primary care (family doctor/general practitioner) or a specialist in the previous year. Additionally, after 6 months, patients were asked about their use of healthcare resources (visits to primary care or specialists and number of days off work in the last 6 months) in a follow-up phone call using several detailed questions.

Baseline clinical characteristics for the ASSESS study were assessed using the mMRC scale for dyspnea (22); the CAT for health status (23); the Hospital Anxiety and Depression Scale (HADS) (24); and the COPD and Asthma Sleep Impact Scale for sleep quality (CASIS) (25, 26). Physical activity levels were also assessed.

Study outcomes

Secondary endpoints in the ASSESS study were the relationship between 24-hour COPD symptoms during the week prior to baseline and the frequency of COPD exacerbations in the year before baseline and during the 6-month follow-up period, and the relationship between 24-hour COPD symptoms and healthcare resource use during both periods.

Statistical analyses

The statistical analyses for baseline demographics and clinical characteristics have been reported previously (20).
The secondary endpoints described above were assessed using univariate analyses. *Post hoc* analyses investigated whether 24-hour symptoms could be used to predict exacerbations during the 6-month follow-up period when confounding factors were controlled. A multivariate analysis was required to address this primary objective, with exacerbation risk as the predicted/dependent variable and variables associated with future exacerbations in univariate analyses as potential (independent) predictors. Initially, a univariate analysis of the relationship between baseline characteristics and exacerbations was employed; variables showing an association with having ≥1 exacerbation during the 6-month follow-up period (at a significance level of *p* ≤ 0.1) were further assessed by multivariate analysis. To select the best subset of predictors, a logistic regression model was fitted including all potential significant factors, applying a forward stepwise variable selection method: each variable was included in the model if it significantly improved model fitting (*p* < 0.05) and was excluded if it significantly worsened model fitting (*p* < 0.10). All statistical analyses were performed using SAS (version 9.1.3 or later; SAS Institute Inc., Cary, NC, USA). For all univariate analyses, a Student’s *t*-test was used for continuous variables, a Mann-Whitney *U* test for ordinal factors and a Chi-square test for categorical parameters. Univariate hypothesis tests were two-sided with no adjustment for multiplicity.

**Results**

**Patient population**

In total, 743 patients were enrolled in the study. Of these, 727 fulfilled the eligibility criteria and completed the Nighttime, Morning and Daytime Symptoms of COPD questionnaire at baseline (full analysis set [FAS] population); 6-month data were available for 698 patients (96.0% of the FAS). The majority of patients were male (65.8%), the mean (standard deviation) age was 67.2 (8.8) years, 27.8% were current smokers, and 72.6% of patients were male (65.8%), the mean (standard deviation) age was 67.2 (8.8) years, 27.8% were current smokers, and 72.6% of patients had moderate or severe airflow limitation (20).

Overall, 67.7% of patients were receiving treatment with an inhaled corticosteroid (ICS), with 66.6% of patients receiving an ICS in combination with a long-acting muscarinic agonist (LAMA) and/or long-acting β2-agonist (LABA) – with or without a phosphodiesterase4 inhibitor. However, over half of these patients (52.7%) may be using an ICS outside its indication, as they had either not experienced any exacerbations within the previous year and/or had forced expiratory volume in 1 second (FEV<sub>1</sub>) ≥60% predicted.

**COPD exacerbations and healthcare resource use during the study**

The proportion of patients with ≥1 exacerbation, the mean number of total exacerbations, and the mean number of visits to primary care (family doctor/general practitioner) or a specialist during the year before baseline and the 6-month follow-up period are shown in Table 1. There was a significant association between patients experiencing exacerbations in the year prior to baseline and patients experiencing exacerbations during the 6-month follow-up period (*p* < 0.001; Table 2).

| Exacerbations during 6-month follow-up | During year before baseline | During 6-month follow-up |
|----------------------------------------|-----------------------------|--------------------------|
| No (N = 333)                           | 258 (57.0)                  | 195 (43.1)               |
| Yes (N = 392)                          | 63 (26.0)                   | 179 (47.0)               |
| *p* < 0.001                            |                            |                          |

**COPD symptoms during each part of the 24-hour day and exacerbations and healthcare resource use during the year before baseline (univariate analyses)**

There was a statistically significant association between symptoms in each part of the 24-hour day and a history of exacerbations in the year before baseline (all *p* < 0.05; Table 3). The mean number of exacerbations in the year before baseline was also significantly higher in patients with nighttime, early-morning or daytime symptoms, compared with patients without symptoms in each corresponding period (all *p* < 0.001; Figure 1a).

There was a statistically significant relationship between nighttime and early-morning symptoms and the frequency of COPD-related visits to the family doctor/general practitioner during the year before baseline (both *p* < 0.001; Table 3). The association between daytime symptoms and visits to primary care did not reach statistical significance. Furthermore, there was no significant relationship between symptoms in any part of the 24-hour day and visits to a specialist during the year before baseline (Table 3).

**COPD symptoms during each part of the 24-hour day and exacerbations and healthcare resource use during the 6 months following baseline (univariate analyses)**

During the week before baseline, 63.0% of patients experienced ≥1 nighttime COPD symptom, 81.4% ≥1 early-morning symptom and 82.7% ≥1 daytime symptom. There was a significant relationship between early-morning and daytime symptoms at baseline and the presence of exacerbations (≥1 exacerbation vs no exacerbations) during the 6-month follow-up period (both *p* < 0.01; Table 3). However, there was no statistically significant association between nighttime symptoms and the presence of exacerbations during this period (Table 3). Symptoms during any part of the 24-hour day were associated with more

### Table 1. COPD exacerbation and healthcare resource use during the year before baseline and in the 6-month follow-up period.

| Exacerbations | During year before baseline | During 6-month follow-up |
|---------------|-----------------------------|--------------------------|
| ≥1 exacerbation, n (%) | 392 (53.9) | 242 (33.3) |
| Number of exacerbations<sup>b</sup> | 1.2 (1.6) | 0.7 (1.5) |
| Healthcare resource use | | |
| Number of visits to primary care | 2.5 (3.3) | 1.0 (1.8) |
| Number of visits to a specialist | 2.0 (2.1) | 0.7 (1.2) |

<sup>a</sup> Percentages based on *N* = 727.

<sup>b</sup> The annualised rate of exacerbations across the 18-month study period was 1.2 (1.6).

All values are mean (SD) unless otherwise indicated.

COPD, chronic obstructive pulmonary disease; SD, standard deviation.

### Table 2. Relationship between presence of exacerbations in the year prior to baseline and during the 6-month follow-up period.

| Exacerbations during 6-month follow-up | No (N = 333) | Yes (N = 392) |
|----------------------------------------|-------------|-------------|
| Exacerbations during previous year | | |
| No | 258 (57.0) | 195 (43.1) |
| Yes | 63 (26.0) | 179 (47.0) |
| *p* < 0.001 | | |
frequent exacerbations (>1 exacerbation vs 0–1 exacerbations; \( p < 0.05 \)). The mean number of exacerbations during the 6-month follow-up period was significantly higher in patients with symptoms in any part of the day compared with patients who had no symptoms (all \( p < 0.05 \); Figure 1b). In addition, there was a significant association between the number of parts of the 24-hour day that a patient experienced COPD symptoms at baseline (none, 1 or 2 parts of the 24-hour day, and 3 parts of the 24-hour day) and the proportion of patients who had an exacerbation during the follow-up period (\( p = 0.010 \)). A higher proportion of patients with \( \geq 1 \) exacerbation during the follow-up period had \( \geq 1 \) symptoms during the whole 24 hours (nighttime, morning and daytime) at baseline (63.6%), compared with patients who did not have an exacerbation (52.8%). There was no significant relationship between symptoms during any part of the 24-hour day and exacerbations requiring hospitalisation during the 6-month follow-up period, although the number of patients with hospitalisations was low (\( p = 0.831, n = 47 \)).

When healthcare resource use during the 6 months following baseline was considered, there was a statistically significant relationship between symptoms during each part of the 24-hour day and the frequency of COPD-related visits to the family doctor/general practitioner (all \( p \leq 0.01 \); Table 3) and between daytime symptoms and COPD-related visits to a specialist (\( p < 0.05 \); Table 3).

The association between other baseline characteristics and exacerbations during the 6-month follow-up period was also assessed (Table 4). In addition to early-morning and daytime symptoms, the following baseline characteristics were all associated with having an exacerbation during the 6-month follow-up period: female gender, not being a current smoker, poor lung function, greater severity of breathlessness, prior history of exacerbations, poor health status (CAT), higher anxiety and depression levels (HADS), poor sleep quality (CASIS), low physical activity level, and a greater number of parts of the day a patient experienced symptoms (all \( p < 0.05 \); Table 4).

### COPD symptoms during each part of the 24-hour day and exacerbations during the 6 months following baseline (multivariate analyses)

The multivariate logistic regression analyses demonstrated, when potential confounding factors were controlled, that 24-hour COPD symptoms were not independent predictors of having an exacerbation during the following 6 months. Only female gender, greater severity of breathlessness, prior exacerbation history and poor health status (CAT) at baseline were independently associated with having an exacerbation during the following 6 months (all \( p < 0.05 \); Table 5). The strongest predictor of having an exacerbation during the follow-up period was an exacerbation during the previous year, with patients with a history of exacerbations approximately 3 times more likely to have an exacerbation during follow-up. Female patients had a 1.6-fold greater likelihood of having an exacerbation than male patients.

A sensitivity analysis in which CAT score was excluded from the

---

**Table 3. The relationship between 24-hour COPD symptoms and the presence of COPD exacerbation and COPD-related healthcare resource use during the year before baseline and the 6-month follow-up period.**

| Nighttime symptoms | Early-morning symptoms | Daytime symptoms |
|--------------------|------------------------|-----------------|
| None               | \( \geq 1 \) symptom    | None            |
| \( \geq 1 \) symptom| \( \geq 1 \) symptom    | None            |

- **During year prior to baseline, \( n \) (%)**
  - \( \geq 1 \) exacerbation (\( n = 392 \))
  - No exacerbation (\( n = 333 \))
  - \( p < 0.01 \)
- **Visits to family doctor**
  - 0 (\( n = 226 \))
  - 1 (\( n = 172 \))
  - \( > 1 \) (\( n = 381 \))
- **Visits to specialist**
  - 0 (\( n = 147 \))
  - 1 (\( n = 172 \))
  - \( > 1 \) (\( n = 381 \))

- **During 6-month follow-up, \( n \) (%)**
  - \( \geq 1 \) exacerbation (\( n = 242 \))
  - No exacerbations (\( n = 453 \))
  - \( p = 0.003 \)
- **Visits to family doctor**
  - 0 (\( n = 380 \))
  - 1 (\( n = 129 \))
  - \( > 1 \) (\( n = 174 \))
- **Visits to specialist**
  - 0 (\( n = 393 \))
  - 1 (\( n = 177 \))
  - \( > 1 \) (\( n = 112 \))

\( n \) = number of patients with available data.

COPD, chronic obstructive pulmonary disease.

---
Discussion

In this study, there was a significant association between early-morning and daytime COPD symptoms at baseline and the proportion of patients who had at least one COPD exacerbation during the following 6 months. However, when potential confounding factors, including lung function and a prior history of exacerbations were taken into account, the association between COPD symptoms in any part of the day and the onset of an exacerbation during the follow-up period was no longer significant. Despite this, patients who had nighttime, early-morning or daytime COPD symptoms also had significantly more COPD exacerbations during the 6-month follow-up period and were more likely to be defined as ‘exacerbators’ (patients with >1 exacerbation). This suggests that although there is a relationship between 24-hour symptoms and the frequency of exacerbations, with symptomatic patients being more likely to experience exacerbations, 24-hour COPD symptoms are not an independent predictor of future exacerbation risk.

When exacerbations and healthcare resource use were considered retrospectively, there was a significant association between nighttime, early-morning and daytime COPD symptoms at baseline and a history of exacerbations. This observation is consistent with previous studies, which have shown that both nighttime and early-morning symptoms were independently associated with a history of exacerbations in the previous...
year (5, 6). One of these earlier studies, however, used multivari- 
ate, rather than univariate, analysis; neither examined the rela-
tionship between symptoms and exacerbation risk prospectively 
to establish if nighttime or early-morning symptoms were also 
associated with a future risk of exacerbation.

An exacerbation during the year before baseline was the 
strongest predictor of an exacerbation during the follow-up 
period in the present study. This is consistent with previous 
studies, such as ECLIPSE, that have also demonstrated that 
patients with a history of exacerbations are most likely to have 
studies, such as ECLIPSE, that have also demonstrated that 
patients with a history of exacerbations are most likely to have 
accompanied by a future risk of exacerbation. However, many of these patients did not 
exhibit the characteristics usually considered to define a high 
risk; 75–80% of patients with FEV₁ ≥ 50% predicted or <2 
year in the past year and 50–64% of patients with FEV₁ ≥ 60% predicted or no exacerbations in the previous year were 
receiving ICS in combination with a LAMA or LABA or both. 
These results are consistent with a large real-life study, which 
demonstrated that approximately half of patients with no his-
tory of exacerbation in the previous year, and who were being 
treated in the primary care setting, were being treated with an 
ICS (32). This suggests that a large proportion of patients with 
COPD who, despite being at low risk of an exacerbation, are 
being treated with ICS. An alternative explanation could be that 
patients who were at risk of an exacerbation are no longer at 
risk of an exacerbation after receiving appropriate maintenance 
treatment.

There are several limitations of the present analysis. Firstly, 
the Nighttime, Morning and Daytime Symptoms of COPD ques-
tionnaire has not been formally validated; at the time of the 
study’s conception, standardized, validated tools for the assess-
ment of symptoms across 24 hours were not available. However, 
since this study was undertaken the concept behind this ques-
tionnaire has been further investigated; a modified version of 
the Nighttime Symptoms of COPD questionnaire (recall period 
24 hours) is being validated and initial validation results have 
been published (33). Furthermore, a version of the Morning 
Symptoms of COPD questionnaire is also in the process of val-
ification (34). Additionally, this study relies on accurate report-
ing of exacerbations and healthcare resource utilisation by the 
patients during the 6-month follow-up phone call.

Conclusions
In the present study, early-morning, daytime and 24-hour 
COPD symptoms were associated with exacerbations during the 
6-month follow-up period and increased healthcare resource use. However, other baseline characteristics including female gender, prior exacerbation history, more severe breathlessness and poor health status were stronger predictors of a future exac-
beration. Nevertheless, from a clinical perspective, these results 
suggest that the presence of 24-hour symptoms has to be con-
sidered as an indicator of the future risk of exacerbations and 
healthcare resource use, thus signalling the need for preventa-
tive measures to be considered. Treatment options that provide 
better overall symptom control and improve health status may 
have clinical benefits in reducing the frequency of exacerbations 
and healthcare resource use.

Acknowledgments
The authors would like to thank all of the patients and their families, the 
team of investigators, research nurses, and operations staff involved in this 
study.

Declaration of interest
This study was funded by Almirall S.A., Barcelona, Spain. The study spon-
sor was involved in the design of the study, analysis and review of the data, 
and review of the manuscript. AstraZeneca reviewed the manuscript for 
accuracy. Medical writing assistance, funded by AstraZeneca, was provided 
by Deborah McGregor, PhD, of Complete Medical Communications (Mac-
clesfield, UK).

Marc Miravitlles has received speaker fees from Almirall, Boehringer 
Ingelheim, Pfizer, AstraZeneca, Chiesi, Esteve, GlaxoSmithKline, Menarini, 
Talecris-Grifols, Takeda-Nycomed and Novartis, and consulting fees from 
Almirall, Boehringer Ingelheim, Pfizer, GlaxoSmithKline, Gebro Pharma, 
MedImmune, Novartis, Talecris-Grifols, Takeda-Nycomed and Teva.

Heinrich Worth has received speaker fees from Almirall, Bayer, 
Boehringer Ingelheim, AstraZeneca, Bionorica, Chiesi, GlaxoSmithKline, 
Klosterfrau, Berlin Chemie, Novartis and Takeda, and consulting fees from 
Almirall, Berlin Chemie, Mundipharma, Bionorica, InterMune, Novartis 
and Takeda.

Table 5. Multivariate analyses of the association between baseline characteristics in 
patients without/with a COPD exacerbation during the 6-month follow-up period.

| Characteristic                        | Odds ratio | 95% CI  | p-value |
|--------------------------------------|------------|---------|---------|
| Female                               | 1.60       | 1.11–2.29 | 0.011 |
| mMRC dyspnoea grade (1-grade increase) | 1.27       | 1.04–1.57 | 0.022 |
| ≥1 COPD exacerbation in the year before baseline | 2.91       | 2.01–4.20 | <0.001 |
| CAT score (1-point increase)         | 1.04       | 1.01–1.07 | 0.005 |

CI, confidence interval; CAT, COPD Assessment Test; COPD, chronic obstructive pul-
monary disease; mMRC, modified Medical Research Council.
Juan José Soler Cataluna has received speaker fees from Almirall, AstraZeneca, Bayer Schering, Boehringer Ingelheim, Esteve, Ferrer, GlaxoSmithKline, Merck, Sharp & Dohme, Novartis, Takeda and Pfizer, and consulting fees from Almirall, Boehringer Ingelheim, Pfizer, GlaxoSmithKline, AstraZeneca, Bayer Schering, Ferrer, Novartis, Merck, Sharp & Dohme, Uriach and Takeda.

David Price has served on advisory boards for Aerocrine, Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis and Teva. He has consultant arrangements with Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Meda, Mundipharma, Napp, Novartis, Pfizer and Teva. He or his research team has received grants (or grants pending) and support for research in respiratory disease from the following organizations in the last 5 years: UK National Health Service, British Lung Foundation, Aerocrine, AstraZeneca, Boehringer Ingelheim, Chiesi, Eli Lilly, GlaxoSmithKline, Meda, Merck, Mundipharma, Novartis, Orion, Pfizer, Respiratory Effectiveness Group, Takeda, Teva and Zenetiva. He has received unrestricted funding for investigator-initiated studies from Aerocrine, AKL Ltd., Almirall, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, Orion, Pfizer, Zenetiva. He or his research team has received payments for lectures/speaking from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Merck, Mundipharma, Novartis, Pfizer, Skyepharma, Takeda and Teva; travel/accommodations/meeting expenses from Aerocrine, Boehringer Ingelheim, Mundipharma, Novartis, Teva, and manuscript preparation from Mundipharma and Teva; and development of educational materials from GlaxoSmithKline and Novartis. He has patents and shares with AKL Ltd. and owns 80% of Research in Real Life Ltd. and its subsidiary social enterprise Optimum Patient Care.

Fernando De Benedetto has received over the past 5 years fees for speaking, participation in advisory boards or consulting from Almirall, Biofutura, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis and Nycomed-Takeda.

Nicolas Roche has received over the past 5 years (i) fees for speaking, organizing education, participation in advisory boards or consulting from Almirall, Altana Pharma-Nycomed-Takeda, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, MEDA, MSD-Chibret, Mundipharma, Novartis, Pfizer and Teva; (ii) research grants from Novartis, Nycomed, Boehringer Ingelheim and Pfizer.

Nina Skavlan Godtfredsen has received, over the past 5 years, fees for participating in advisory boards or consulting from Almirall, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Nycomed-Takeda and Sandoz, and research grants from Boehringer Ingelheim.

Thys van der Molen has received, over the past 5 years, payments for lectures and advisory boards from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Merck, Mundipharma and Teva. His institution has received grants for research from The Lung Foundation Netherlands, Stichting bestrijding Astma, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Merck, Mundipharma, Novartis and Nycomed.

Claes-Göran Löfdahl has received some reimbursement for lectures and ad hoc advisory boards from Almirall, AstraZeneca, Boehringer Ingelheim, Novartis and Takeda.

Laura Padullés is an employee of Almirall S.A., Barcelona, Spain. Anna Ribera is an employee of AstraZeneca PLC, Barcelona, Spain, and a former employee of Almirall S.A., Barcelona, Spain.

References

1. van der Molen T, Miravitlles M, Kocks JW. COPD management: role of symptom assessment in routine clinical practice. Int J Chron Obstruct Pulmon Dis 2013; 8:461–471.

2. Partridge MR, Karlsson N, Small IR. Patient insight into the impact of chronic obstructive pulmonary disease in the morning: an internet survey. Curr Med Res Opin 2009; 25:2043–2048.

3. Espinosa de los Monteros MJ, Pena C, Soto Hurtado EJ, Jareno J, Miravitlles M. Variability of respiratory symptoms in severe COPD. Arch Bronconeumol 2012; 48:3–7.

4. Agusti A, Hedner J, Marin JM, Barbe F, Cazzola M, Rennard S. Night-time symptoms: A forgotten dimension of COPD. Eur Respir Rev 2011; 20:183–194.

5. Price D, Small M, Milligan G, Higgins V, Garcia Gil E, Estruch J. Impact of night-time symptoms in COPD: a real-world study in five European countries. Int J Chron Obstruct Pulmon Dis 2013; 8:595–603.

6. Roche N, Small M, Broomfield S, Higgins V, Pollard R. Real world COPD: Association of morning symptoms with clinical and patient reported outcomes. COPD 2013; 10:679–686.

7. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease [Internet]. [updated 2016; cited 2015 Apr 16]. Available from: http://www.goldcopd.org/uploads/users/files/GOLD_Report2014_Feb07.pdf.

8. Anzueto A, Leimer I, Kesten S. Impact of frequency of COPD exacerbations on pulmonary function, health status and clinical outcomes. Int J Chron Obstruct Pulmon Dis 2009; 4:245–251.

9. Miravitlles M, Ferrer M, Pont A, Zalacain R, Alvarez-Sala JL, Masa F, et al. Effect of exacerbations on quality of life in patients with chronic obstructive pulmonary disease: a 2 year follow up study. Thorax 2004; 59:387–395.

10. Halpin DM, Decramer M, Celli B, Kesten S, Liu D, Tashkin DP. Exacerbation frequency and course of COPD. Int J Chron Obstruct Pulmon Dis 2012; 7:653–661.

11. Soler-Cataluna JJ, Martinez-Garcia MA, Roman SP, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax 2005; 60:925–931.

12. Toy EL, Gallagher KF, Stanley EL, Swensen AR, Duh MS. The economic impact of exacerbations of chronic obstructive pulmonary disease and exacerbation definition: A review. COPD 2010; 7:214–228.

13. Miravitlles M, Garcia-Polo C, Domenech A, Villegas G, Conget F, de la Roza C. Clinical outcomes and cost analysis of exacerbations in chronic obstructive pulmonary disease. Lung 2013; 191:523–530.

14. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med 2010; 363:1128–1138.

15. Moy ML, Teylan M, Weston NA, Gagnon DR, Garshick E. Daily step count predicts acute exacerbations in a US cohort with COPD. PLoS One 2013; 8:e60400.

16. Beek KM, Glaab T, Stowasser S, Schmidt H, Fabbri LM, Rabe KF et al. Characterisation of exacerbation risk and exacerbator phenotypes in the POET-COPD trial. Respir Res 2013; 14:116.

17. Burgel PR, Nemes-Meyer P, Chanez P, Carré P, Perez T et al. Cough and sputum production are associated with frequent exacerbations and hospitalizations in COPD subjects. Chest 2009; 135:975–982.

18. Niewoehner DE, Lokhnygina Y, Rice K, Kuschnier WG, Sharafkhaneh A, Sarosi GA, et al. Risk indexes for exacerbations and hospitalizations due to COPD. Chest 2007; 131:20–28.

19. Quint JK, Baghai-Ravary R, Donaldson GC, Wedzicha JA. Relationship between depression and exacerbations in COPD. Eur Respir J 2008; 32:53–60.

20. Miravitlles M, Worth H, Soler Cataluna JJ, Price D, De Benedetto F, Roche N et al. Observational study to characterise 24-hour COPD symptoms and their relationship with patient-reported outcomes: results from the ASSESS study. Respir Res 2014; 15:122.

21. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease [Internet]. [updated 2016; cited 2014 Oct 20]. Available from: http://www.goldcopd.org/Guidelines/guideline-2016-gold-report.html.

22. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999; 54:581–586.
23. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. Eur Respir J 2009; 34:648–654.
24. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67:361–370.
25. Pokrzywinski RF, Meads DM, McKenna SP, Glendenning GA, Revicki DA. Development and psychometric assessment of the COPD and Asthma Sleep Impact Scale (CASIS). Health Qual Life Outcomes 2009; 7:98.
26. Miravitlles M, Iribarri M, Barrueco M, Lleonart M, Villarrubia E, Galera J. Usefulness of the LCOPD, CAFS and CASIS scales in understanding the impact of COPD on patients. Respiration 2013; 86:190–200.
27. Celli B, Vestbo J, Jenkins CR, Jones PW, Ferguson GT, Calverley PM et al. Sex differences in mortality and clinical expressions of patients with chronic obstructive pulmonary disease. The TORCH experience. Am J Respir Crit Care Med 2011; 183:317–322.
28. Naberan K, Azpeitia A, Cantoni J, Miravitlles M. Impairment of quality of life in women with chronic obstructive pulmonary disease. Respir Med 2012; 106:367–373.
29. Kerkhof M, Freeman D, Jones R, Chisholm A, Price DB. Predicting frequent COPD exacerbations using primary care data. Int J Chron Obstruct Pulmon Dis 2015; 10:2439–2450.
30. Di Marco F, Verga M, Reggente M, Maria CF, Santus P, Blasi F et al. Anxiety and depression in COPD patients: The roles of gender and disease severity. Respir Med 2006; 100:1767–1774.
31. Kessler R, Partridge MR, Miravitlles M, Cazzola M, Vogelmeier C, Leynaud D et al. Symptom variability in patients with severe COPD: A pan-European cross-sectional study. Eur Respir J 2011; 37:264–272.
32. Price D, West D, Brusselle G, Gruffydd-Jones K, Jones R, Miravitlles M et al. Management of COPD in the UK primary-care setting: An analysis of real-life prescribing patterns. Int J Chron Obstruct Pulmon Dis 2014; 9:889–904.
33. Mocarski M, Zaiser E, Trundell D, Make BJ, Hareendran A. Evaluation of the psychometric properties of the Nighttime Symptoms of COPD Instrument. Int J Chron Obstruct Pulmon Dis 2015; 10:475–487.
34. Mocarski M, Hareendran A, Jen MH, Zaiser E, Make BJ. Evaluation of the psychometric properties of the early morning symptoms of COPD instrument (EMSCI). Value Health 2014; 17 (3): A179.