A comparison of COPD patients with and without ACOS in the ECLIPSE study

To the Editor:

There is growing interest in asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS) [1, 2]. Yet, there is no consensus on the best definition of ACOS [1, 2] and, therefore, it is difficult to appropriately characterise these patients. Here, we compare the main clinical characteristics and outcomes of COPD patients with and without ACOS in the ECLIPSE cohort [3] according to six different definitions of ACOS.

The design and methodology used in the ECLIPSE study (ClinicalTrials.gov identifier: NCT00292552; GSK study code SCO104960) have been published elsewhere [3]. ECLIPSE was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committees of participating centres. All participants signed their written consent [3].

The current analysis is restricted to COPD patients (n=1976, 91.3% of the total population studied in ECLIPSE) with a recorded response to the question in the ATS-DLD-78A questionnaire "Have you ever had asthma?" [4]. For the primary study definition, COPD patients answering "yes" were considered to have ACOS. Besides, we considered five additional features of airways disease in conjunction to ACOS: 1) presence of bronchodilator reversibility at recruitment (change in forced expiratory volume in 1 s (FEV_1) $\geqslant$12% and $\geqslant$200 mL); 2) presence of current asthma (affirmative answer to two questions: "Have you ever had asthma?" and "Do you still have it?"); 3) presence of wheeze (affirmative answer to the question "Does your chest ever sounds wheezy or whistling?"); 4) presence of atopy (affirmative answer to the question "Have you ever had hay fever?"); and 5) presence of both wheeze and atopy.

Results are presented as n (%), mean±SD or median (IQR), as appropriate. Groups were compared using the Wilcoxon and Chi-squared tests for continuous and categorical variables, respectively. Negative binomial regression (risk ratios) and multiple regression (least squared mean differences) were used to compare clinically relevant outcomes (exacerbations during follow-up and St George Respiratory Questionnaire (SGRQ) scores) in patients with and without ACOS, after adjustment for age, sex, baseline FEV_1 % and previous exacerbation history. Patients with missing post-bronchodilator FEV_1 (or any other missing covariate) were not included in the adjusted analyses.

The main results (table 1) showed that 493 (25%) patients had ACOS according to the primary definition used, and 462 (94%) of them reported that their diagnosis of asthma had been confirmed by a doctor. Patients with ACOS were slightly younger, more often female, had a longer duration of COPD and used respiratory medications and statins more often. They had slightly less cumulative smoking exposure but the proportion of former smokers was similar between groups. The prevalence of chronic bronchitis and emphysema was also similar, as was the average FEV_1 before and after bronchodilation. The proportions of co-morbidities were higher in ACOS patients (66% had at least one of osteoporosis, osteoarthritis, reflux/heartburn, depression requiring treatment or anxiety/panic attacks, compared with 43% in COPD patients without ACOS). They also had a higher proportion of autoimmune disease (11% had rheumatoid arthritis and inflammatory bowel diseases, compared with 5% in those without ACOS). The reported prevalence of cardiovascular diseases was similar in both groups. The circulating levels of eosinophils and several inflammatory biomarkers (determined as detailed elsewhere [5]) were also similar between groups except for plasma fibrinogen, which was higher in patients with ACOS (table 1).

After adjusting for age, sex, baseline FEV_1, and prior exacerbation history, the SGRQ total score was higher in patients with ACOS (LS mean difference 3.1, 95% confidence interval 1.2–5.0). Adjusted exacerbation rates during follow-up were also more frequent in patients with ACOS (RR 1.32, 95% CI 1.19–1.46). Mortality rates during follow-up were similar in COPD patients with (10%) and without (9%) ACOS.

Among the 493 patients that reported ever having had asthma, 432 (88%) also reported wheeze, 353 (72%) reported current asthma, 135 (27%) reported atopy and 127 (26%) reported both wheeze and atopy. Demographics and clinical characteristics of patients stratified according to these additional features were similar to those of patients with ACOS as defined by the primary definition alone (data not shown). On the other hand, 111 patients with ACOS (23%) had significant bronchodilator reversibility (as defined above).

TABLE 1 Main clinical characteristics

	COPD	ACOS	p-value
Patients n (%)	1483 (75)	493 (25)	
Age years	63.8±6.9	62.3±7.7	<0.01
Sex females n (%)	447 (30)	226 (46)	<0.01
COPD duration ⩾10 years n (%)	456 (31)	203 (41)	<0.01
Body mass index kg·m^{-2}	26.3±5.5	27.0±6.1	0.08
Inhaled steroids n (%)	1022 (69)	403 (82)	<0.01
Long-acting β_2 agonist n (%)	944 (64)	398 (81)	<0.01
Long-acting muscarinic antagonist n (%)	641 (43)	255 (52)	<0.01
Statin n (%)	322 (22)	134 (27)	0.01
Smoking history pack-years	49.8±26.9	45.4±27.4	<0.01
Former smoker n (%)	942 (64)	317 (64)	0.76
Chronic bronchitis n (%)	539 (36)	157 (32)	0.07
Emphysema n (%)	1236 (94)	452 (95)	0.44
FEV_1 % reference			
Pre-bronchodilator	44.1±14.7	43.5±15.4	0.29
Post-bronchodilator	48.3±15.5	47.9±16.2	0.55
Eosinophils ×10^9·L^{-1}	0.18 (0.17)	0.18 (0.17)	0.22
Eosinophils ×10^9·L^{-1} n (%)			0.41
<150	559 (39)	172 (36)	
150–300	579 (40)	199 (42)	
>300	293 (20)	108 (23)	
White blood cells ×10^9·L^{-1}	7.60 (2.70)	7.60 (2.50)	0.73
Neutrophils ×10^9·L^{-1}	4.92 (2.30)	4.88 (2.09)	0.31
Fibrinogen mg·dL^{-1}	444 (130)	462 (122)	<0.01
Surfactant protein D ng·mL^{-1}	122 (90)	115 (81)	0.12
Club cell secretory protein ng·mL^{-1}	5.03 (3.44)	4.91 (3.75)	0.53
High sensitivity CRP mg·L^{-1}	3.20 (5.70)	3.10 (5.50)	0.74
IL-6 pg·mL^{-1}	1.55 (2.32)	1.49 (2.48)	0.48
IL-8 pg·mL^{-1}	7.15 (10.20)	7.10 (8.70)	0.47
CCL-18 pg·mL^{-1}	104 (54)	108 (52)	0.30
TNF-α pg·mL^{-1}	2.35 (4.70)	2.35 (22.95)	<0.01

Data are presented as mean±SD or median (interquartile range), unless otherwise stated. COPD: chronic obstructive pulmonary disease; ACOS: asthma–COPD overlap syndrome; CRP: C-reactive protein; IL: interleukin; CCL-18: chemokine ligand 18; TNF: tumour necrosis factor.

Although the number of patients in this group is small, it seemed to include fewer females, patients with COPD duration greater than 10 years, and patients with lower SGRQ total scores (data not shown).

These findings confirm prior research demonstrating that patients with ACOS are younger, and more likely to be female, report more symptoms, experience more exacerbations and have worse health-status than COPD patients [6–10]. We found that BMI was similar between groups (table 1) also in keeping with prior literature [7, 9] with the exception of an National Health and Nutrition Examination Survey study that noted a higher proportion of obese patients with ACOS [11]. The fact that patients with ACOS had a lower smoking exposure is also consistent with published studies [7, 12]. Previous reports found significantly higher concentrations of blood and sputum eosinophils in ACOS patients [12], but we could not reproduce these observations. By contrast, we found that plasma fibrinogen and serum TNF-α concentration were slightly higher in ACOS, an observation that is consistent with its association with worse outcomes in COPD [5].

Our study provides two novel observations of potential relevance, depicted in figure 1. First, symptoms and exacerbations were higher among ACOS patients than COPD patients, irrespective of their severity of airflow limitation, age, sex, lung function and exacerbation history. Secondly, we found that patient demographics and clinical characteristics did not differ substantially when the diagnosis of ACOS was established using several different definitions. Yet, it has some limitations that deserve comment. First, because ECLIPSE patients were mostly recruited in secondary and tertiary hospitals, results may not be generalisable to milder COPD or patients in primary care. Secondly, many of the study characteristics are based on patient self-report. Thirdly, our airflow limitation reversibility categorisation considered reversibility status at recruitment only, whereas it may vary with time [13]. Fourth, almost all patients included in ECLIPSE were of Caucasian origin (98%), so our ability to examine a potential ethnic effect

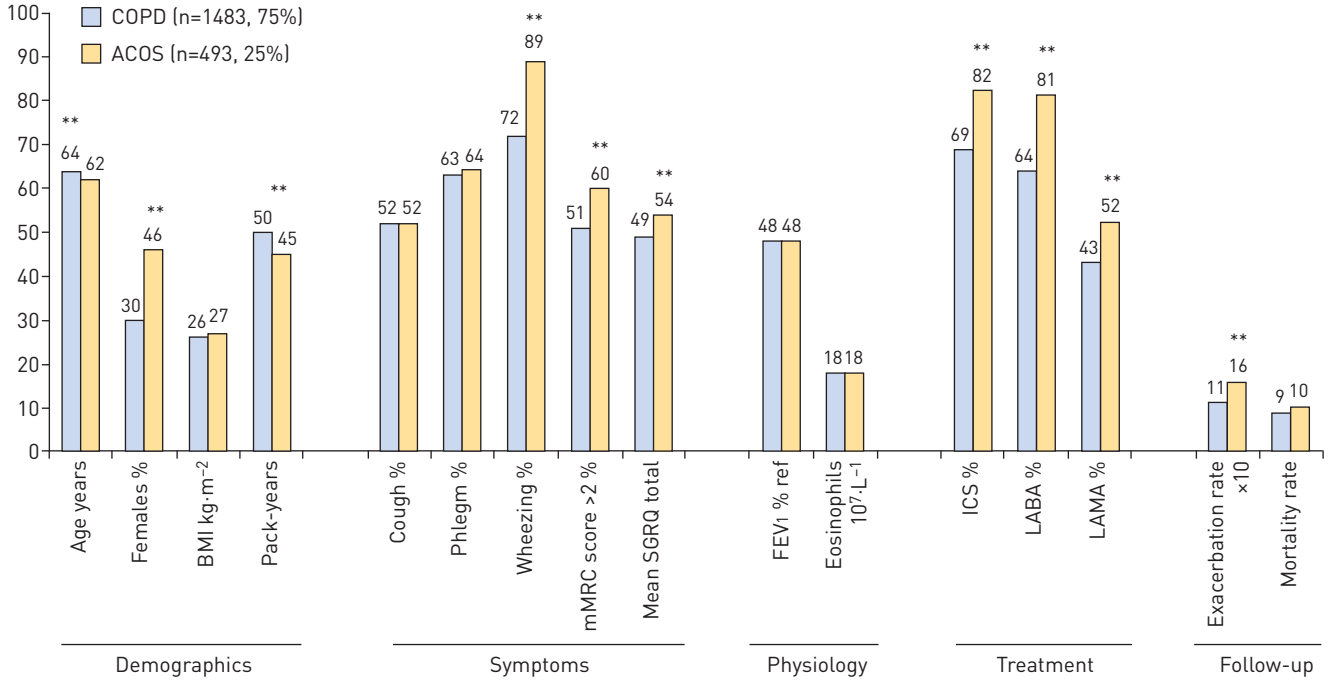

FIGURE 1 Comparison of the main demographic, symptom, physiological, therapeutic and follow-up differences observed between chronic obstructive pulmonary disease (COPD) and asthma–COPD overlap syndrome (ACOS) patients. BMI: body mass index; mMRC: modified Medical Research Council dyspnoea scale; SGRQ: St George Respiratory Questionnaire; FEV_1: forced expiratory volume in 1 s; ICS: inhaled corticosteroid; LABA: long-acting β_2 agonist; LAMA: long-acting muscarinic antagonist. **: p<0.01.

was limited. Finally, the molecular basis of the observed differences between ACOS and COPD is unclear and deserves specific focus in future research.

In summary, these results help to better characterise ACOS and suggest that its primary definition is not sensitive to the addition of specific clinical criteria related to asthma. These findings may assist in the development of optimal strategies for the definition and management of ACOS, as ACOS patients may need closer medical supervision.

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Blood eosinophil count to predict bronchial eosinophilic inflammation in COPD

To the Editor:

Chronic obstructive pulmonary disease (COPD) is an inflammatory disease of the airways. There is evidence that maintenance treatment with inhaled corticosteroids (ICS) in COPD results in a reduction in the mean rate of exacerbations, and improvement in quality of life and lung function [1]. However, ICS therapy has been associated with increased risk of oropharyngeal candidiasis, hoarseness and pneumonia [1]. In COPD, ICS are now recommended in cases of frequent exacerbations and severe obstruction [2].

Even if neutrophilic inflammation is conspicuous in the airways of most COPD and related to the severity of airway obstruction [3], some patients may exhibit raised airway eosinophilic inflammation [4, 5], and those patients show the greater response to a short course of oral [4] and inhaled corticoids [6]. A strategy that focused on sputum eosinophils to adjust dose of ICS and oral glucocorticoids in COPD proved to reduce exacerbation and hospitalisation [7]. Given the difficulty of applying the technique of induced sputum in clinical practice, there is a need to find a biomarker to identify sputum eosinophils in COPD, as has been done in asthma.

Raised blood eosinophil count is a common finding in COPD (37.4% with persistent blood eosinophil count $\geqslant$2%) [8] and seems a promising biomarker to predict the response of COPD patients to ICS [9, 10]. Furthermore, blood eosinophil count >2% during an exacerbation was found to predict the utility of systemic corticoids to accelerate recovery [11]. Likewise, this threshold predicted that chronic treatment with ICS added to long-acting β-agonists (LABA) would prevent exacerbation [9]. Clinical benefit from maintenance treatment with ICS in COPD has recently been found to be particularly clear when the blood eosinophil count was >280 per μL [10].

In contrast to asthma, there are no data in the literature on the ability and thresholds of blood eosinophil count to reflect bronchial eosinophilic inflammation in COPD.

We conducted a retrospective study of 155 consecutive COPD patients seen at the COPD clinic of a university hospital (CHU Sart-Tilman, Liege, Belgium), where COPD was defined as a post-bronchodilation forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio <70%. Patients filled in the COPD Assessment Test (CAT) questionnaire and underwent exhaled nitric oxide fraction (F_{eNO}) measurement followed by spirometry, sputum induction and blood sampling on the same day during a 1-h visit. Data are