

# Inhaled corticosteroid use by exacerbations and eosinophils: a real-world COPD population

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**Background:** Blood eosinophils may predict response to inhaled corticosteroids (ICS) in chronic obstructive pulmonary disease (COPD) where ICS is recommended in patients at high risk of exacerbations. The proportion of patients who may benefit the most from ICS-based therapy was quantified in a real-world population.

**Materials and methods:** European data from the Adelphi Real World Respiratory Disease Specific Programme™ 2017 survey were collected from consecutive COPD patients by participating physicians. Overall, 1,528 patients were assessable for Global Initiative for COPD (GOLD) 2017 status and were included in the analysis.

**Results:** More GOLD D patients had elevated eosinophil counts compared with GOLD B. The proportions of GOLD D patients with a history of  $\geq 2$  exacerbations and eosinophil counts of  $\geq 150$ ,  $\geq 300$ , and  $\geq 400$  cells/ $\mu\text{L}$  were 81.2%, 39.4%, and 24.6%, respectively. In total, 10.6% of the patients had  $\geq 300$  eosinophils/ $\mu\text{L}$  and a history of  $\geq 2$  exacerbations. ICS-based therapy was received by 41.5% of GOLD B and 68.0% of GOLD D patients.

**Conclusion:** There was no apparent relation between ICS use and eosinophil blood count. There are differences in the distributions of patients with frequent exacerbations and/or high blood eosinophil counts and the use of ICS in COPD. These data may provide information for the implementation of future treatment recommendations.

**Keywords:** COPD, exacerbations, inhaled corticosteroids, eosinophils, observational study

## Introduction

The clinical benefits versus risks of inhaled corticosteroids (ICS) in the treatment of chronic obstructive pulmonary disease (COPD) have been disputed. Initially widely prescribed, since 2011, they are now recommended for symptomatic patients at high risk of exacerbations by the Global Initiative for COPD (GOLD) Strategy.<sup>1,2</sup> Putative concerns over ICS in the treatment of COPD include increased risks of pneumonia, oral candidiasis and hoarseness, and possibly hyperglycemia, osteoporotic fractures, and cataracts.<sup>3</sup> It is therefore important to limit ICS exposure to those patients likely to benefit. Nevertheless, ICS remain widely prescribed in combination with a long-acting  $\beta_2$ -agonist (LABA), or both a LABA and long-acting muscarinic agonist (LAMA) (“triple” therapy),<sup>4–7</sup> and the over-prescription of ICS in COPD has been widely reported.<sup>4,6–10</sup>

The GOLD Strategy document revision of 2017 includes changes that reduce the recommended use of ICS.<sup>2</sup> Recognizing the limitations of forced expiratory volume in 1 second (FEV<sub>1</sub>) in predicting the risk of exacerbations, spirometry has been removed from the ABCD classification process for deciding management. Consequently, patients with more symptoms who were also previously considered

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high risk (group D) solely due to impaired lung function have now been reclassified as low risk (group B), for whom ICS are not recommended.<sup>2</sup>

In GOLD 2017 group D, the preferred initial prescription for COPD patients without concomitant asthma is LABA plus LAMA therapy, with the addition of ICS in patients with continued exacerbations.<sup>2</sup> However, it is probable that ICS responders form a subset of the COPD population. Evidence is emerging that blood eosinophil counts in COPD patients may predict response to ICS.<sup>11–18</sup> For example, a secondary analysis of data from two parallel randomized controlled trials showed that reductions in exacerbations with fluticasone furoate/vilanterol, compared with vilanterol alone, were more prominent with increasing blood eosinophil counts.<sup>11</sup> Similar findings were reported when comparing beclomethasone/formoterol with formoterol only.<sup>12</sup> A post-hoc analysis of the large WISDOM study (n=2,296) also demonstrated that withdrawal of ICS in patients previously receiving triple therapy was associated with an increased risk of exacerbations only in those who had an eosinophil count  $\geq 300$  cells/ $\mu$ L and a history of exacerbations.<sup>18</sup> Finally, when comparing triple therapy with tiotropium, the effect on risk of exacerbations was more pronounced in patients with an eosinophil count above 200 cells/ $\mu$ L or 2% than in patients with lower eosinophil counts.<sup>19</sup> Data from the FLAME study showed that indacaterol/glycopyrronium provided superior or similar benefits to salmeterol/fluticasone in reducing the risk of exacerbations, regardless of blood eosinophil levels in patients with COPD;<sup>13</sup> however, there was a significant interaction between treatment effect and blood eosinophil levels with the two treatments demonstrating similar efficacy in patients with blood eosinophils  $\geq 300$  cells/ $\mu$ L.<sup>17</sup>

It may therefore be possible to define which COPD patients may significantly benefit from ICS-based therapy based on exacerbation history and blood eosinophil counts. Such data may be extracted through analysis of a real-life data set. The Adelphi Real World Disease Specific Programme™ (DSP) is a large multinational, cross-sectional survey that generates observational real-world data from current clinical practice.

The aim of this analysis is to report the proportion of COPD patients in the DSP who had a history of 0, 1, or  $\geq 2$  exacerbations in the last 12 months, with additional stratification by blood eosinophil levels and GOLD 2017 grouping. The study will also describe the clinical characteristics and current treatment patterns of the COPD patients who may benefit from ICS-based therapy.

## Methods

Cross-sectional data collected via physician and patient surveys undertaken by the Respiratory DSP 2017 data were collected in the first three months of the year and are representative of COPD patients presenting to their physician in a routine care setting. The methodology has been published previously.<sup>20,21</sup> In brief, data were collected from primary care physicians (PCPs) and pulmonologists and their patients in five European countries (France, Germany, Italy, Spain, and the UK). To be eligible to participate, PCPs and pulmonologists had to manage  $>3$  patients each week, be actively involved in COPD management and have been medically qualified between 1979 and 2012. Inclusion criteria for patients were a physician-confirmed airflow obstruction and a current diagnosis of COPD (including emphysema and/or chronic bronchitis).

Each participating physician completed a patient record form for the next five consecutive patients with COPD who consulted them for any reason (not necessarily COPD). The same patients then voluntarily completed details relating to their condition via a patient self-completion form (PSC). Although not truly random, the study physicians had no control over which of the eligible patients in their care presented in their clinic during the data collection period, and physician pre-selection of patients was thereby limited. Prescription of long-acting bronchodilators and ICS were not regulated in this study. Patients were excluded at the analysis stage if they were subsequently found to have a diagnosis or history of asthma.

Primary patient variables extracted for analysis were exacerbation frequency and severity in the previous 12 months, blood eosinophil count, and current treatment group. Exacerbations were physician-confirmed and were recorded regardless of severity. Exacerbations extracted for analysis were presented as moderate (treated with oral/systemic corticosteroids or antibiotics) or severe (requiring hospitalization). To qualify as high risk for exacerbations, as described by GOLD 2017, patients suffered  $\geq 2$  moderate or severe exacerbations, or  $\geq 1$  severe exacerbation (requiring hospitalization), in the previous 12 months.<sup>2</sup> An eosinophil count was described as high according to two thresholds:  $\geq 300$  cells/ $\mu$ L and  $\geq 400$  cells/ $\mu$ L, as defined by previous studies.<sup>12,17,18,22</sup> Descriptive variables, including GOLD 2017 group, COPD Assessment Test (CAT) score,<sup>23</sup> modified Medical Research Council Dyspnea

Scale (mMRC),<sup>24</sup> and most recent post-bronchodilator FEV<sub>1</sub>% predicted, were also collected, as previously described.<sup>21</sup>

The full Respiratory DSP XV (2017) sample size conducted in the EU comprised of 600 physicians (300 PCPs and 300 pulmonologists). These physicians completed patient record form data on 3,003 COPD-only patients. Patients with a concomitant diagnosis of asthma were excluded from the analysis (n=127), producing a maximum study population of 2,876 with full exacerbation and treatment history in the last 12 months.

Data are presented as patient proportions and summary statistics.

The DSP was conducted as a survey adhering to market research guidelines and codes of conduct according to the International Chamber of Commerce/European Society for Opinion and Marketing Research international code on observational research. Before completing the voluntary PSC, patients were asked to provide written consent. Physicians and patients provided anonymized data. The survey was submitted to the Freiburger Ethik-Kommission International (FEKI) where approval was granted on 25th January 2017 (FEKI Code 017/1014).

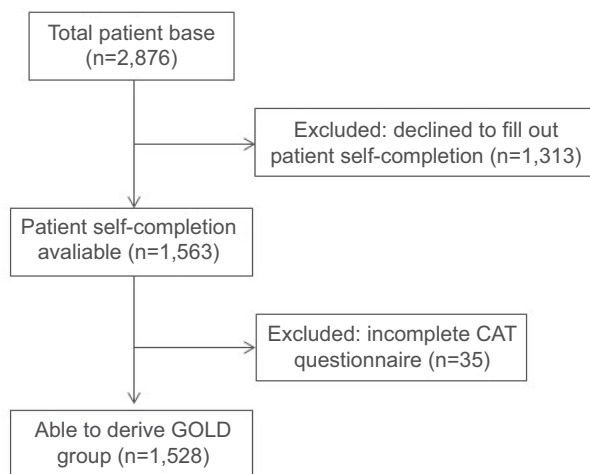
## Results

### Patient baseline characteristics

Of the 2,876 patients included, 1,563 supplied the accompanying self-completion form and represent the maximum study population where patient-reported data is given. Of these, 1,528 were assessable for GOLD 2017 group status, calculated by using physician-reported recent history of exacerbations and patient-reported CAT scores (Figure 1). Baseline characteristics are presented in Table 1.

The mean age of the population was 66 years; approximately 70% of patients were male. Almost all were current or ex-smokers, with high past or present tobacco consumption. As expected, the patient population had many comorbidities, approximately two-thirds presenting with hypertension alone. Patients in groups A, B, C, and D constituted 12.0%, 61.1%, 0.9%, and 26.0% of the population, respectively, and did not differ significantly between primary care physicians and pulmonologists. As patients were predominantly GOLD B or D, we focused on comparisons between these two groups.

Regarding post-bronchodilator FEV<sub>1</sub>% predicted, 33.8% of GOLD D patients had values <50%. In GOLD B patients, the corresponding figure was 11.0%.



**Figure 1** Patient disposition.

**Abbreviation:** CAT, COPD Assessment Test.

### Exacerbation rates by GOLD 2017 group

The proportions of COPD patients who had a history of 0, 1, 2, or  $\geq 3$  exacerbations in the last 12 months in GOLD groups B and D are shown in Figure 2. As per definition, all GOLD B patients experienced <2 exacerbations (mean, 0.2) during this period. In contrast, the mean number of exacerbations in GOLD D was 2.3, and 83.8% of GOLD D patients experienced  $\geq 2$  exacerbations. This figure additionally shows that almost 80% of GOLD B patients experienced no exacerbations over the study period, and, by definition, no patients in this group suffered a severe exacerbation. In the GOLD D group, one-quarter of patients experienced  $\geq 3$  exacerbations, and 58% suffered  $\geq 1$  severe exacerbation. In total, 41.6% of GOLD D patients experienced moderate exacerbations only.

### Eosinophil blood count distribution by GOLD group and exacerbation frequencies

Where both data variables were available, mean eosinophil counts in GOLD B and D groups were 257.3 (n=205) and 294.0 (n=147) cells/ $\mu$ L, respectively. Numerically, greater proportions of patients in GOLD D group had elevated cell counts compared with the GOLD B group ( $\geq 150$  cells/ $\mu$ L, 79.7% vs 73.8%;  $\geq 300$  cells/ $\mu$ L, 37.8% vs 30.5%;  $\geq 400$  cells/ $\mu$ L, 23.6% vs 19.2%).

Figure 3 shows the proportions of COPD patients with histories of 0, 1, or  $\geq 2$  of total and severe exacerbations by blood eosinophil levels. There was a numerical trend for higher proportions of patients with eosinophil counts of  $\geq 300$  cells/ $\mu$ L with a history of 1 (41.0%) or  $\geq 2$  (39.4%)

**Table 1** Baseline characteristics of all EU patients with derived GOLD classification (n=1,528)

Parameter	Total (n=1,528)	GOLD A (n=183)	GOLD B (n=935)	GOLD C (n=13)	GOLD D (n=397)
Mean age, mean	65.7	61.7	65.8	65.3	67.4
Male/female, %	68.2/31.8	73.8/26.2	65.0/35.0	92.3/7.7	72.3/27.7
Mean body mass index, kg/m <sup>2</sup>	26.7	26.7	26.6	27.1	26.9
Current smokers, %	30.2	23.2	29.3	9.1	36.2
Pack years ≥10, % of current smokers	95.1	92.7	95.6	100.0	94.7
Ex-smokers, %	62.5	71.3	62.1	90.9	58.4
Pack years ≥10, % of ex-smokers	97.7	95.2	98.2	100.0	97.7
Employment status, %					
Retired	63.5	53.7	60.3	84.6	74.8
working full time	18.0	30.5	19.5	15.4	9.2
Homemaker	9.4	9.6	11.3	0.0	5.3
Unemployed	6.0	3.4	5.6	0.0	8.4
Working part time	2.9	2.8	3.2	0.0	2.3
Current comorbidities, % <sup>a</sup>					
Hypertension	67.2	53.9	66.0	58.3	76.5
Elevated cholesterol/hyperlipidemia	28.9	26.1	25.6	33.3	37.5
Diabetes	15.3	13.3	13.3	58.3	19.6
Anxiety	13.6	6.1	11.8	0.0	21.7
Gastroesophageal reflux disease (GERD)	10.9	6.1	10.6	0.0	14.0
Mean time since diagnosis, months	62.2	38.6	57.9	40.6	84.5
Mean CAT score	20.2	5.8	20.9	7.1	25.7
mMRC score					
0–1	59.6	95.1	62.3	53.8	36.4
2–4	40.4	4.9	37.7	46.2	63.6
Mean post-bronchodilator FEV <sub>1</sub> (% predicted)	64.6	74.7	66.5	61.0	56.6
Mean post-bronchodilator FEV <sub>1</sub> /FVC	0.58	0.62	0.60	0.53	0.54
Mean frequency of hospitalizations in last 12 months	0.2	0.0	0.0	0.2	0.9

**Note:** <sup>a</sup>Present in >10% of the total population.

**Abbreviation:** CAT, COPD Assessment Test.

exacerbations compared with no exacerbations (25.0%). In contrast, there was no apparent relation for eosinophil blood count distribution by the number of previous severe exacerbations. The proportions of patients with a history of 1 or ≥2 severe exacerbations and an eosinophil count of ≥300 cells/μL were 35.8% and 29.3%, respectively. The proportion of patients with an eosinophil blood count of ≥300 cells/μL and with a history of ≥2 moderate/severe exacerbations in the overall study population was 10.6%.

## Current treatment patterns by GOLD group and eosinophil blood count distribution

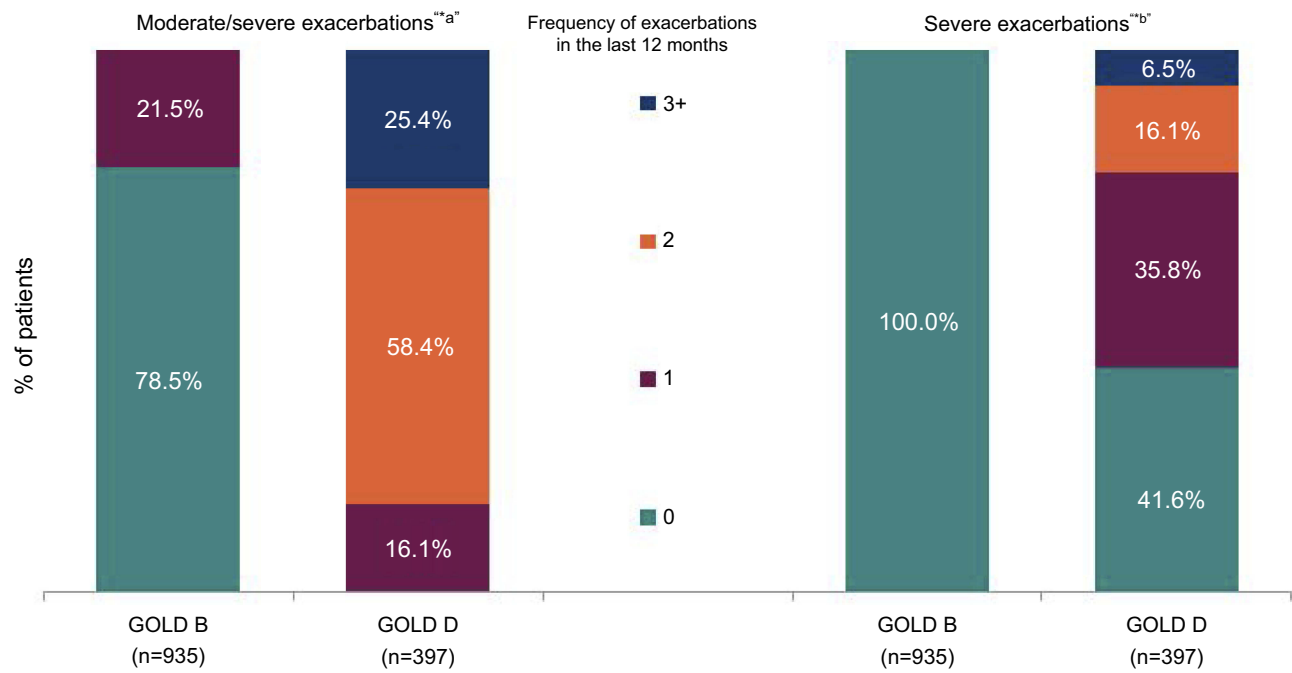
Current treatment patterns by GOLD group are shown in Figure 4. ICS-based therapy was being received by 41.5% of GOLD B patients and 68.0% of GOLD D patients. There was no clear difference between patients seen by primary

care physicians or pulmonologists, although primary care physicians tended to treat patients classified as GOLD B with more ICS, 45.7% vs 38.5%. Almost half of GOLD D patients were receiving triple therapy. In total, 56.2% of GOLD B patients were receiving mono or dual bronchodilator therapy. A minority of GOLD D patients (8.6%) were taking mono or short-acting only bronchodilator therapy.

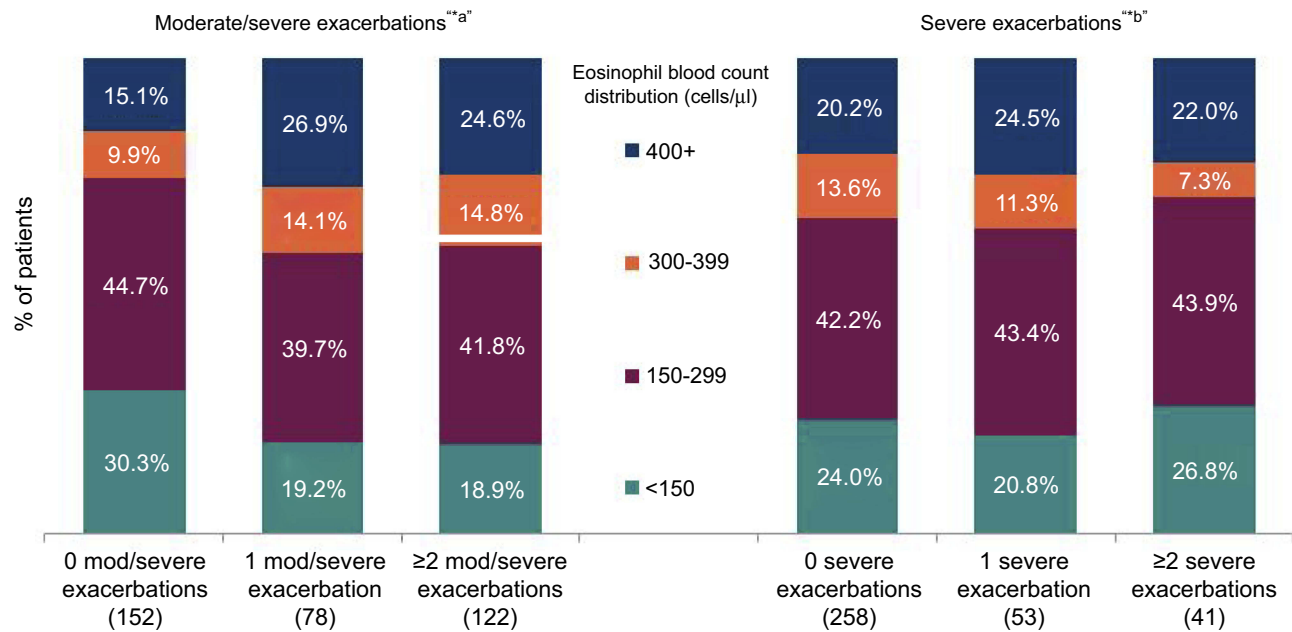
The percentages of patients receiving ICS therapy by exacerbation rates (any) and by eosinophil blood count distribution are shown in Figure 5. The data show that ICS use increased with higher rates of exacerbations, but that there was no apparent relation between ICS use and eosinophil blood count.

## Discussion

This study, performed in a large real-world data set of patients with COPD, provided detailed information

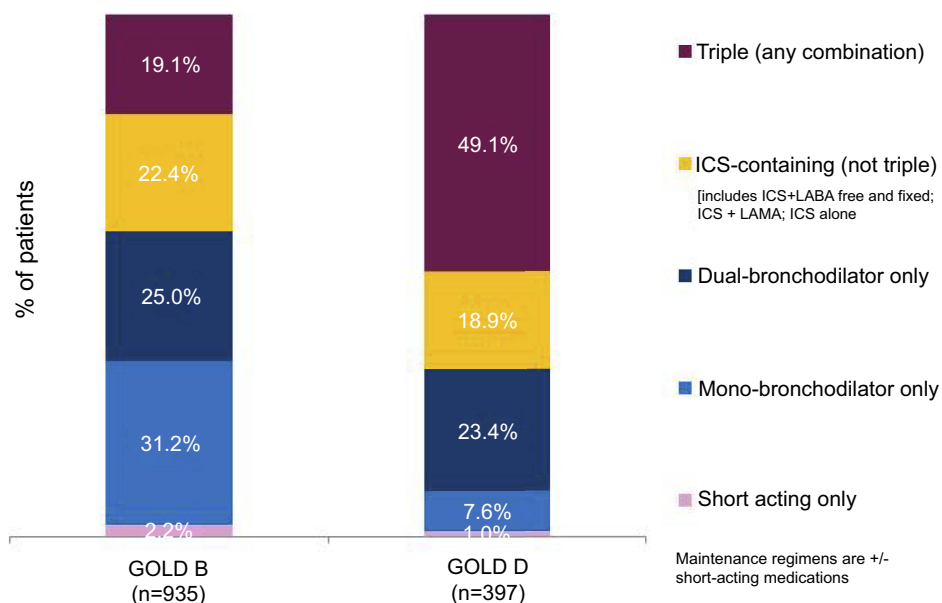


**Figure 2** The proportions of chronic obstructive pulmonary disease (COPD) patients with a history of 0, 1, 2, or  $\geq 3$  exacerbations in the previous 12 months in Global Initiative for COPD (GOLD) groups B and D. <sup>\*\*</sup>Exacerbations which required treatment with oral corticosteroids, antibiotic, and/or hospital admission. <sup>\*\*\*</sup>Exacerbations which required hospital admission. Population: All EU COPD-only patients with a derived GOLD group (calculated by using physician-reported recent history of exacerbations and patient-reported CAT score).  
**Abbreviation:** CAT, COPD Assessment Test.



**Figure 3** The proportions of chronic obstructive pulmonary disease patients with histories of 0, 1, or  $\geq 2$  of total and severe exacerbations by eosinophil blood count distribution. <sup>\*\*</sup>Exacerbations which required treatment with OCS, antibiotic, and/or hospital admission. <sup>\*\*\*</sup>Exacerbations which required hospital admission. Population: All EU COPD-only patients with a derived GOLD group (calculated by using physician-reported recent history of exacerbations and patient-reported CAT score) and a stated eosinophil blood count.  
**Abbreviation:** CAT, COPD Assessment Test.





**Figure 4** Current treatment patterns by Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) group. Population: All EU COPD-only patients with a derived GOLD group (calculated by using physician-reported recent history of exacerbations and patient-reported CAT score).

**Abbreviation:** CAT, COPD Assessment Test.

	0 exacerbations	1 exacerbation	≥2 exacerbations
Eosinophil count <150 cells/μL	34.8% (n=46)	60.0% (n=15)	82.6% (n=23)
Eosinophil count ≥150 cells/μL	35.8% (n=106)	60.3% (n=63)	72.7% (n=99)
Eosinophil count ≥300 cells/μL	23.7% (n=38)	43.8% (n=32)	75.0% (n=48)

**Figure 5** The percentages of patients receiving inhaled corticosteroid treatment by exacerbation rate and by eosinophil blood count. Population: All EU COPD-only patients with a stated eosinophil blood count and known recent history of exacerbations.

regarding clinical characteristics, exacerbation history, and eosinophil blood count distribution across GOLD 2017 groups B and D. It also showed that a minority of patients overall presented both as high risk (GOLD group D) and with high blood eosinophil levels ( $\geq 300$  cells/ $\mu\text{L}$ ) and that many “low-risk” patients (GOLD group B) and blood eosinophil levels  $< 300$  cells/ $\mu\text{L}$  received ICS.

The current study population predominantly fell into GOLD 2017 highly symptomatic groups B and D, as reflected by a mean CAT symptom score of  $> 20$ . In the present study, as previously noted for this DSP and other populations, these data may indicate that COPD is frequently undiagnosed unless the patient is highly symptomatic.<sup>21,25,26</sup>

The GOLD 2017 group distribution in the current study differs from the GOLD 2011 distribution in a previous study of this DSP<sup>21</sup> in that the proportion of GOLD B patients was considerably larger and that for GOLD D patients was correspondingly smaller. This resulted

from patients previously considered group D due to impaired lung function alone under the GOLD 2011 classification being reclassified as group B under the new GOLD classification.<sup>2</sup> This has been observed in other cohorts.<sup>27,28</sup>

According to the GOLD 2017 Strategy, ICS-based treatment is preferred only for patients classified as group D.<sup>2</sup> In the present study, these patients were not only more likely to experience  $\geq 2$  exacerbations and/or be hospitalized in the previous 12 months, by definition, but were also more burdened by COPD symptoms, poor lung function, and comorbidities. More than half of group D patients suffered  $\geq 1$  severe exacerbation. Each exacerbation requiring hospitalization has been shown to cause a decline in health and raise the risk of further severe exacerbations.<sup>29</sup> A parallel worsening in symptoms, air-flow limitation, and exacerbation incidence in more severe disease has previously been noted for this DSP.<sup>21</sup> A link between COPD risk under the 2011 GOLD Strategy and

incidence of comorbidities has been reported in other studies.<sup>25,30</sup>

There was a clear contrast between group D patients and group B patients, many of whom experienced no exacerbations, confirming their low-risk status. Although the mean eosinophil blood count and the proportion of patients with blood counts  $\geq 300$  cells/ $\mu\text{L}$  were higher in group D patients versus group B patients; the differences in blood count distribution between these groups were not marked. Further examination showed that there was a similar modest difference in blood count distribution between patients experiencing  $< 2$  and  $\geq 2$  exacerbations, as may be expected from the GOLD group data. The greatest differences in blood eosinophil count distribution were seen between that for patients with no exacerbations and those for patients with 1 or  $\geq 2$  in the previous 12 months, which is not reflected by GOLD grouping.<sup>2</sup> There was no apparent relation between eosinophil blood count distribution and number of severe exacerbations.

In a Danish study, compared with lower eosinophil levels, a blood count of  $\geq 340$  cells/ $\mu\text{L}$  was associated with a 76% adjusted increase in risk for severe exacerbations and a 15% increase for moderate exacerbations.<sup>31</sup> More recently, a retrospective survey found that, after adjustment, significantly greater numbers of exacerbations were found in patients with blood eosinophil counts of  $\geq 300$ ,  $\geq 400$ , and  $\geq 500$  cells/ $\mu\text{L}$  compared with those with counts lower than each of these respective thresholds.<sup>32</sup> However, in the FLAME study, there was no relation found between blood eosinophil count and the rate of moderate/severe exacerbations in the overall study population.<sup>13</sup> It should be noted, however, that in this latter study, for patients with blood eosinophil counts of  $< 300$  cells/ $\mu\text{L}$ , indacaterol/glycopyrronium significantly reduced the rate of moderate/severe exacerbations compared with salmeterol/fluticasone in patients with 1 and  $\geq 2$  exacerbations ( $p < 0.001$  and  $p = 0.038$ , respectively), whereas the effects of both treatments were similar in patients with blood eosinophil counts of  $\geq 300$  cells/ $\mu\text{L}$ , independent of exacerbation history.<sup>17</sup> The study data therefore support the contention that blood eosinophil levels are a marker of response to ICS.

It is possible that a clear relation between eosinophil blood count and exacerbation history was not observed in the present study due to the widespread prescription of ICS, which may have suppressed exacerbations – or eosinophils – in some patients. Indeed, some patients classified as group B may have been “masked” group D patients, whose exacerbations were controlled by the long-term (ie,  $> 12$  months)

administration of ICS. Data from the FLAME study again showed long-term ICS therapy to have had a minimal effect on blood eosinophil levels,<sup>13</sup> but given the large number of studies examining baseline eosinophil counts and response to ICS, there is a scarcity of studies examining the effects of different ICSs at different doses on blood eosinophils.

Data from the present study show that treatment with ICS bears no relation to eosinophil blood count distribution. This may be expected as currently there is no strong recommendation for considering eosinophil levels when deciding treatment.<sup>2</sup> However, the present data show that ICS-based treatment was being received by over half of all patients with blood counts of  $< 300$  cells/ $\mu\text{L}$ , and even  $< 150$  cells/ $\mu\text{L}$ , who may be less likely to benefit from these therapies.<sup>18</sup> Indeed, the proportion of patients with an eosinophil blood count of  $\geq 300$  cells/ $\mu\text{L}$  and a history of  $\geq 2$  moderate/severe exacerbations was under 11% of the total COPD population in our study.

Recent evidence has shown that it is possible in appropriate patients receiving long-acting bronchodilators, to withdraw ICS without increasing the overall risk of exacerbations. The WISDOM study showed that most patients with eosinophil counts  $< 300$  cells/ $\mu\text{L}$  receiving triple therapy were able to discontinue ICS without experiencing increased exacerbations.<sup>18</sup> An analysis of data from the DACCORD observational study showed that in appropriate patients in real-life clinical practice, it was possible to change treatment from ICS/LABA or triple therapy to LABA/LAMA therapy without increased exacerbations.<sup>33</sup>

In 2017, two new fixed-dose combination (FDC) triple therapy formulations were licensed.<sup>34,35</sup> The active comparators in the pivotal trials for these formulations were ICS/LABA or LAMA alone. The first comparison between FDC triple therapy and a LABA/LAMA combination included symptomatic patients with  $\geq 1$  exacerbation in the previous year and found that FDC triple therapy was superior to LABA/LAMA in reducing the rate of moderate-to-severe exacerbations by 15%, the effect being more pronounced in those with a baseline eosinophil count of  $\geq 200$  cells/ $\mu\text{L}$  (19%) versus those with lower counts (13%).<sup>17</sup> The second comparison found that FDC was superior to LABA/LAMA in reducing the rate of moderate-to-severe exacerbations (25% reduction). The effect was also more pronounced in this study in patients with a baseline eosinophil count of  $\geq 150$  cells/ $\mu\text{L}$  (32%) compared to those with lower counts (12%).<sup>36</sup>

Regarding study limitations, given the difficulties in differentiating diagnoses of specific respiratory diseases, it is conceivable an unknown proportion of patients may have

been incorrectly diagnosed with COPD. However, this is common to most real-world surveys and unlikely a significant problem. In addition, the GOLD A-D classification is meant mainly to decide initial treatment and we cannot preclude that a number of patients in Group B are actually not Group D patients originally who have subsequently responded to treatment. Furthermore, the sample collected is not a truly random sample of COPD patients. Therefore, it may inaccurately represent the overall COPD patient population. Lastly, for tests not routinely conducted or available, a sizable amount of missing data is to be expected. Therefore, generalizability is unknown as the assumption that the missing data reflects the data collected cannot be confirmed. Despite these limitations, real-world data collected without pre-selection of patients and mandatory measurement of disease characteristics make a valuable contribution to understand COPD disease.

## Conclusion

In conclusion, this real-world study data indicate that there are differences in the distributions of patients with frequent exacerbations and/or high blood eosinophil counts and the use of ICS in COPD. Only a minority of the overall patient population presented both as high risk ( $\geq 2$  exacerbations) and with high ( $\geq 300$  cells/ $\mu\text{l}$ ) blood eosinophil levels. These data may provide information for the implementation of future treatment recommendations.

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## Disclosure

JV reports personal fees from AstraZeneca, grants, Boehringer-Ingelheim, Chiesi, and Novartis, outside the

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