



# Withdrawal of inhaled corticosteroids in COPD: a European Respiratory Society guideline

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This ERS short guideline summarises the evidence and provides recommendations for ICS withdrawal in patients with COPD <https://bit.ly/33R3M5w>

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**ABSTRACT** Inhaled corticosteroids (ICS) combined with bronchodilators can reduce the frequency of exacerbations in some patients with chronic obstructive pulmonary disease (COPD). There is evidence, however, that ICS are frequently used in patients where their benefit has not been established. Therefore, there is a need for a personalised approach to the use of ICS in COPD and to consider withdrawal of ICS in patients without a clear indication. This document reports European Respiratory Society recommendations regarding ICS withdrawal in patients with COPD.

Comprehensive evidence synthesis was performed to summarise all available evidence relevant to the question: should ICS be withdrawn in patients with COPD? The evidence was appraised using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach and the results were summarised in evidence profiles. The evidence synthesis was discussed and recommendations formulated by a committee with expertise in COPD and guideline methodology.

After considering the balance of desirable and undesirable consequences, quality of evidence, and feasibility and acceptability of interventions, the guideline panel made: 1) conditional recommendation for the withdrawal of ICS in patients with COPD without a history of frequent exacerbations, 2) strong recommendation not to withdraw ICS in patients with blood eosinophil counts  $\geq 300$  eosinophils- $\mu\text{L}^{-1}$  and 3) strong recommendation to treat with one or two long-acting bronchodilators if ICS are withdrawn.

A conditional recommendation indicates that there was uncertainty about the balance of desirable and undesirable consequences of the intervention, and that well-informed patients may make different choices regarding whether to have or not have the specific intervention.

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## Introduction

The use of inhaled corticosteroids (ICS) combined with long-acting bronchodilators (LABDs) is recommended for prevention of exacerbations in patients with moderate to very severe chronic obstructive pulmonary disease (COPD) [1]. However, several studies have shown extensive use of ICS in patients in which they may not be indicated [2–5]. This inappropriate use of ICS may be associated with an increased risk of side-effects, in particular in the COPD population, which usually consists of elderly subjects with several comorbidities and high prevalence of frailty [6–8]. These side-effects include an increased risk of pneumonia, mycobacterial disease, increased incidence and poor control of diabetes, osteoporosis and bone fractures, dysphonia and oropharyngeal candidiasis, among others [9–12].

Results of recent clinical trials and observational studies indicate that not all patients with COPD benefit from the use of ICS. In particular, those patients with recurrent exacerbations and higher concentrations of sputum or blood eosinophils demonstrated a better response to ICS, while patients with low blood eosinophil concentrations showed no response to ICS and may be at a higher risk of complications [13–18].

The lack of response to ICS in some COPD patients, the extensive use of ICS in patients in which they are not indicated and the possibility of development of side-effects with the long-term use of these drugs have generated interest in the investigation of the possible consequences and benefits of ICS withdrawal. Initial studies of ICS withdrawal in COPD were small and the alternative treatment was either placebo or short-acting bronchodilators (SABDs) [19–24]; in contrast, more recent studies included large populations of patients with withdrawal to either one or two LABDs [25, 26].

The interest in ICS withdrawal in COPD is reflected in the publication of two meta-analyses [27, 28] and several position papers that describe algorithms for the identification of the right patients for discontinuation [5, 29–34]. Moreover, ICS withdrawal has recently been recognised as a potential therapeutic option in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy [1].

The purpose of this Task Force was to develop a recommendation that answers the following question: should ICS be withdrawn in patients with COPD? This guideline employed a systematic review of the literature followed by the application of the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach [35].

## Methods

### *Group composition*

This document has been developed following the requirements for guidelines of the European Respiratory Society (ERS) [36]. The guideline panel co-chairs (J.D.C. and M.M.) were selected by the ERS. They led all aspects of project management and selected the guideline panel, which included 10 clinicians and researchers with experience in COPD, one ERS Early Career Member representative, two ERS methodologists and a patient representative. A methodology group consisting of two panel members (I.F.L. and J.D.C.) under the supervision of the ERS methodologist (D.R.) identified and collected the evidence, performed the evidence syntheses, constructed the evidence profiles and ensured that all the methodological requirements were met. The co-chairs and panellists discussed the evidence and formulated the recommendations. The guideline was developed using the short guideline format with guideline development completed within 12 months and addressing a single PICO (patient, intervention, comparator, outcomes) question that is considered to be of special clinical interest.

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### **Formulation of question**

Guideline panel members agreed on the formulation of the PICO question [37]. P: patients with COPD. I: withdrawal of ICS with continuation of LABDs. C: continuation of ICS. O: exacerbation frequency, respiratory hospitalisations, quality-of-life measures, adverse effects, pneumonia, healthcare resource utilisation, all-cause hospitalisation, forced expiratory volume in 1 s (FEV<sub>1</sub>), use of reliever medication, dyspnoea, exercise capacity and all-cause mortality.

The guideline panel pre-specified that within the population they would examine subgroups based on baseline FEV<sub>1</sub>, blood eosinophil count and history of frequent exacerbations, if such data were available.

### **Rating the importance of outcomes**

After defining the question, the guideline panel identified outcomes that they considered relevant to it. They rated the importance of each outcome using a scale from 1 to 9 (a rating of 1–3 was assigned to outcomes of low importance, 4–6 to important outcomes and 7–9 to outcomes critically important for decision making).

### **Literature searches**

The methodology group conducted a systematic review and meta-analysis of studies according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) recommendations [38]. At the first guideline panel meeting the inclusion and exclusion criteria were agreed upon. Studies included were randomised controlled trials that compared the continuation of ICS and ICS withdrawal in outpatients with stable COPD. COPD was defined as per the GOLD definition [1]. The panel determined that for inclusion in the meta-analysis the ICS withdrawal groups had to be prescribed an alternative LABD therapy, which is the current standard of care [1]. The follow-up period for study inclusion was a minimum of 6 months based on the majority opinion of the panel that most clinically relevant outcomes could not be evaluated within a shorter study duration.

Full details of the literature search and systematic review are described in the supplementary material.

### **Evidence synthesis**

Studies were finally selected for inclusion *via* consensus decision of three authors (I.F.L., J.D.C. and M.M.) after review of the full text and the selection was approved by the full panel. Data collection was performed independently by two authors (I.F.L. and J.D.C.) in a blinded fashion for all outcomes of interest. They collected the data in a pre-designed spreadsheet for consistency and the data were checked by two other authors (M.M. and D.R.). Exacerbation rates were determined *via* three measures (exacerbation frequency, time to first exacerbation and number of patients experiencing at least one exacerbation). Severe exacerbations were defined as those requiring hospitalisation. Quality of life was measured with the St Georges Respiratory Questionnaire (SGRQ). Symptoms were measured *via* dyspnoea scores and the Transition Dyspnoea Index.

Study characteristics, types of participants, interventions, outcomes measured and results were extracted from each study. If the data were amenable to pooling, effects were estimated *via* meta-analysis using Review Manager version 5 (<https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman>). For the meta-analyses, the random effects model was utilised unless otherwise specified. Dichotomous outcomes were reported as relative risks and continuous outcomes were reported as mean differences unless otherwise specified. The methodology team appraised the quality of evidence using the GRADE approach [39] and a GRADE approach for deprescribing [35].

GRADEpro was used to develop evidence profiles that summarised the findings for each outcome and the rationale for the quality of evidence appraisal [37]. Thresholds for clinically important changes (used to judge imprecision) included the following relative risk reductions: mortality 15%, exacerbations 20%, hospitalisations 20%, treatment failure 20% and adverse events 15%. They also included the following absolute reductions: SGRQ score change of 4 points and FEV<sub>1</sub> change of 100 mL. The thresholds for clinically important relative risk reductions were based upon the Task Force's collective clinical experience. The thresholds for clinically important absolute risk reductions were based upon published literature [40]. Details of the statistical analysis are described in the supplementary material.

### **Formulating and grading recommendations**

Recommendations were formulated on the basis of the following considerations: the balance of desirable (benefits) and undesirable consequences (burden, adverse effects and cost) of the intervention, the quality of evidence, patient values and preferences, and feasibility [41].

A strong recommendation was made for an intervention when the panel was certain that the desirable consequences of the intervention outweighed the undesirable consequences, just as a strong recommendation would have been made against an intervention if the panel was certain that the undesirable consequences of the intervention outweighed the desirable consequences. A strong recommendation indicates that most well-informed patients would choose to have or not to have the intervention.

A conditional recommendation was made for an intervention when the panel was uncertain that the desirable consequences of the intervention outweighed the undesirable consequences, just as a conditional recommendation would have been made against an intervention if the panel was uncertain that the undesirable consequences of the intervention outweighed the desirable consequences. Reasons for uncertainty included low or very low quality of evidence, the desirable and undesirable consequences being finely balanced or the underlying values and preferences playing an important role. A conditional recommendation indicates that well-informed patients may make different choices regarding whether to have or not to have the intervention. Recommendations were formulated using the GRADE Evidence to Decision framework.

In one area identified as important by the panel but not suitable for formal ratings of quality of evidence, *i.e.* the modalities of ICS withdrawal, good practice statements were produced as per GRADE guidance [42].

### Manuscript preparation

The initial draft of the manuscript and the supplementary material were prepared by the first authors (J.D.C. and I.F.L.) and edited by the chairs and methodologist. Both the manuscript and the supplementary material were reviewed, edited and approved by all panel members prior to submission.

## Results

### Should ICS be withdrawn in patients with COPD?

Patients treated with ICS should be evaluated by recording the frequency of exacerbations and hospitalisations along with measurement of the blood eosinophil count to aid decision making with the following recommendations summarised in Figure 1.

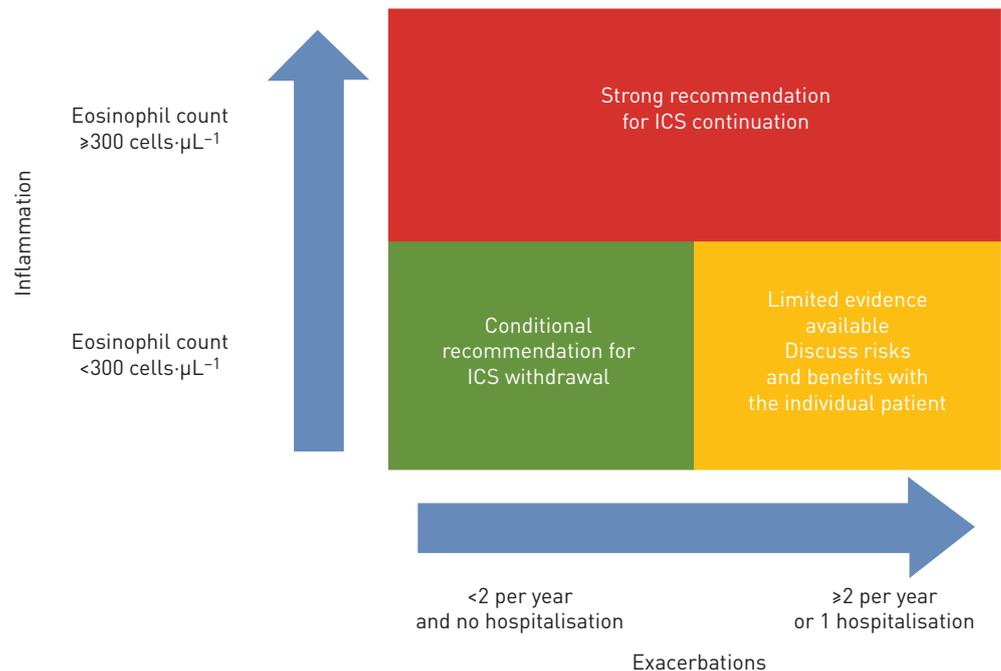


FIGURE 1 Summary of the guideline recommendations. ICS: inhaled corticosteroid. We recommend taking account of prior exacerbation history and blood eosinophil counts. Patients with a high rate of exacerbations and eosinophil counts  $>300$  cells· $\mu\text{L}^{-1}$  should not be considered for ICS withdrawal. Patients not meeting these criteria may be candidates for ICS withdrawal.

### Recommendations

- 1) For patients with COPD without a history of frequent exacerbations consider ICS withdrawal (conditional recommendation, moderate quality of evidence).
- 2) We recommend not to withdraw ICS in patients who have a blood eosinophil count  $\geq 300$  eosinophils- $\mu\text{L}^{-1}$ , with or without a history of frequent exacerbations (strong recommendation, moderate quality of evidence).
- 3) If ICS are withdrawn, patients should be treated with one or two LABDs (strong recommendation, moderate quality of evidence).

For patients with COPD and a history of frequent exacerbations but  $< 300$  eosinophils- $\mu\text{L}^{-1}$ , no recommendation can be formulated due to a lack of evidence. Note that patients without a history of frequent exacerbations are those with no more than one moderate exacerbation in the previous year.

Our literature search found that three studies stopped ICS abruptly while one study withdrew gradually. The absence of meaningful differences in outcomes between these studies suggests that ICS can be abruptly withdrawn in the majority of cases.

### Good practice point

Monitoring of exacerbation frequency, symptoms and lung function is recommended following ICS withdrawal. Some patients may deteriorate following any change in treatment, including ICS withdrawal. Therefore, ongoing monitoring is appropriate.

### Summary of the evidence

Full details of the literature search that informed the guideline development are provided in the supplementary material. We identified a total of 1603 papers; once duplicates were removed, the total was 1385. Ultimately, four studies met all inclusion and no exclusion criteria and were included in the meta-analysis: COSMIC [21], WISDOM [25], INSTEAD [43] and SUNSET [26]. All four trials were funded by the pharmaceutical industry.

The total number of patients in the four trials was 4492. Patients were included in all four studies if they were aged  $>40$  years with a history COPD defined as having had a smoking history of at least 10 pack-years and a post-bronchodilator FEV<sub>1</sub>/forced vital capacity ratio  $< 0.70$  (COSMIC used 88% or 89% of predicted according to sex). Patients with moderate to very severe COPD and stable disease status with the absence of exacerbation during the screening or run-in periods were included. Patients with other respiratory disorders, particularly asthma, or on long-term oxygen therapy were excluded. The majority of patients recruited were not frequent exacerbators, with the exception of the patients recruited to the COSMIC study who were required to have had at least two exacerbations in the previous year [21].

There was variability in the treatment strategies and ICS use prior to recruitment to the studies. The COSMIC trial had a run-in period of 12 weeks where patients were treated with salmeterol/fluticasone propionate (SFC) 50/500  $\mu\text{g}$  twice daily. The groups were then assigned to either continuing SFC or switching to salmeterol 50  $\mu\text{g}$  twice daily for 1 year [20]. Patients recruited to the INSTEAD trial were included if they had received treatment with SFC 50/500  $\mu\text{g}$  for at least 3 months prior to screening. After a 14-day run-in period, the participants were randomised to continue the SFC therapy or switch to indacaterol 150  $\mu\text{g}$  once daily for 26 weeks [42]. At the time of screening for the WISDOM trial, patients were given triple therapy (SFC 50/500  $\mu\text{g}$  twice daily and tiotropium 18  $\mu\text{g}$  once daily) for a run-in period of 6 weeks. They were then randomised to either continue triple therapy or have the fluticasone reduced in a stepwise manner over the first 12 weeks and continued on the assigned therapy until 12 months of follow-up [24]. Not all participants in the WISDOM trial were receiving ICS therapy prior to the run-in period. The SUNSET trial recruited patients who had been on triple therapy for at least 6 months prior to screening. Patients were all given SFC 50/500  $\mu\text{g}$  twice daily with tiotropium 18  $\mu\text{g}$  daily during a 4-week run-in period before being randomised to either continue triple therapy or switch to indacaterol/glycopyrronium once daily for 26 weeks [25].

Meta-analyses were performed on the outcomes rated as critical and the subgroup analysis on baseline eosinophils. There was insufficient data to perform subgroup analyses on FEV<sub>1</sub> and prior exacerbation frequency due to a lack of data. The results are summarised in the following sections and a full description is provided in the supplementary material. Data for important outcomes were extracted and are presented in the supplementary material.

### Critical outcomes: benefits and harms

#### Exacerbation end-points

The meta-analysis found that ICS withdrawal was not associated with an increased frequency of exacerbations. The effect estimate for frequency of moderate or severe exacerbations was rate ratio (RR)

(per patient per year) 1.05 (95% CI 0.97–1.13;  $p=0.23$ ,  $I^2=0\%$ ) over 6 or 12 months with no significant difference between ICS withdrawal and continuation. Time to first moderate or severe exacerbation was measured in three studies [25, 26, 43] with no effect of ICS withdrawal (hazard ratio (HR) 1.04 (95% CI 0.94–1.16;  $p=0.42$ ,  $I^2=2\%$ )). For the number of patients experiencing at least one moderate or severe exacerbation, which was reported in two studies [21, 43], there was no significant effect (OR 0.84 (95% CI 0.63–1.14;  $p=0.26$ ,  $I^2=0\%$ )).

For the end-point of hospitalisation for severe exacerbations we did not perform a meta-analysis as there were only data from two studies [25, 43]. In the INSTEAD study, ICS withdrawal had an OR of 0.49 (95% CI 0.04–5.43;  $p=0.56$ ) favouring ICS withdrawal; however, there were very few patients with severe exacerbations ( $n=1$  ICS withdrawal and  $n=2$  ICS continuation). The WISDOM study measured time to first severe exacerbation, which resulted in a HR of 1.20 (95% CI 0.98–1.48;  $p=0.08$ ) for ICS withdrawal.

The number of patients with at least one severe exacerbation was considered a critical outcome, but information about this variable was available in only one study. In addition, this study included stable patients and the number of events was extremely low. Despite grading this outcome with low quality of evidence, we believe that it does not downgrade the overall quality of evidence of the recommendation.

#### *Quality of life*

The SGRQ was used in all four studies and the pooled mean difference between the two arms was  $-0.87$  points (95% CI  $-1.72$ – $-0.02$  points;  $p=0.05$ ,  $I^2=21\%$ ), suggesting a very small and clinically insignificant worsening in quality of life [21, 25, 26, 43].

#### *Adverse effects*

There were no statistically significant differences between ICS withdrawal and continuation in the number of patients experiencing adverse events in the pooled analysis of three studies (OR 0.94 (95% CI 0.82–1.08;  $p=0.41$ ,  $I^2=55\%$ )) [25, 26, 43]. Hospitalisations for serious adverse events were similar between the two groups in the WISDOM study: 271 out of 1242 (21.8%) *versus* 273 out of 1243 (21.9%) for ICS withdrawal *versus* continuation, respectively [25].

#### *Pneumonia*

Three studies provided data on pneumonia that were suitable for meta-analysis. The results were not statistically significant (OR 0.89 (95% CI 0.64–1.22;  $p=0.46$ ,  $I^2=0\%$ )). Absolute numbers of pneumonia events were low: 74 out of 1792 (4.13%) in the ICS withdrawal group and 83 out of 2057 (4.04%) in the ICS continuation group [25, 26, 43].

#### *FEV<sub>1</sub>*

FEV<sub>1</sub> was classified as important but not critical for decision making by the panel. In the COSMIC study, there was a significant reduction in pre-dose FEV<sub>1</sub> after the ICS run-in period with an adjusted difference of 4.1 percentage points favouring ICS continuation. The absolute difference between the two arms of the study after 12 months was 50 mL (95% CI 10–100 mL;  $p=0.022$ ) [21].

In the WISDOM study, the adjusted mean reduction in trough FEV<sub>1</sub> from baseline to end of the study at week 52 was an adjusted mean reduction of 43 mL greater in the ICS withdrawal group [25].

In INSTEAD study, the least squares mean difference was  $-0.009$  L (95% CI  $-0.045$ – $-0.026$  L), which was not statistically significant. It was reported that there were no significant differences between the groups at other time-points during the study [43].

At the end of the SUNSET study (day 182), the difference in least squares mean for trough FEV<sub>1</sub> from baseline was  $-26$  mL (95% CI  $-53$ – $-1$  mL;  $p=0.0573$ ). There was a consistently lower mean trough FEV<sub>1</sub> in the ICS withdrawal group compared with the ICS continuation group and the results were statistically significant until day 181 [26].

#### *Use of rescue medication*

The mean percentage of rescue medication-free days in the COSMIC study was 47% (SE 2%) in the ICS withdrawal group and 53% (SE 2%) in the continuation group ( $p=0.014$ ) [21]. In the INSTEAD study, the percentage of rescue medication-free days was 52.8% *versus* 54.6% ( $p=0.505$ ) in the ICS withdrawal and continuation groups, respectively [43]. The mean change in puffs per day of rescue medication was  $-0.44$  *versus*  $-0.49$ , respectively, with a difference of 0.05 (95% CI  $-0.17$ – $-0.28$ ;  $p=0.650$ ) [42]. In the SUNSET study, the difference in puffs per day between the two arms was 0.177 (95% CI  $-0.01$ – $-0.36$ ) and the difference in rescue medication-free days between the two arms was 0.103 (95% CI  $-3.25$ – $-3.25$ ) [26].

*Dyspnoea*

No clinically significant differences were observed in measures of dyspnoea in the reported studies. Results are summarised in the supplementary material.

*All-cause mortality*

Overall, all-cause mortality was low in the three studies in which it was reported and there were no significant differences between the two groups (supplementary material).

*Other end-points*

No data was presented for types of exacerbations, healthcare resource utilisation, all-cause hospitalisations or exercise capacity.

*Subgroup analyses*

Of the pre-specified subgroups to examine, data were only available for blood eosinophil counts in more than one study (WISDOM and SUNSET) [25, 26, 44]. The most significant findings were when comparing baseline eosinophils of  $<300$  to  $\geq 300$  cells· $\mu\text{L}^{-1}$  on moderate or severe exacerbation rates between the ICS withdrawal and continuation groups.

In patients with eosinophil counts  $<300$  cells· $\mu\text{L}^{-1}$  there was no effect of ICS withdrawal on exacerbation rate (RR 1.03 (95% CI 0.90–1.18;  $p=0.71$ ,  $I^2=0\%$ )), but there was a significant increase in exacerbations in patients with eosinophil counts  $\geq 300$  cells· $\mu\text{L}^{-1}$  (RR 1.63 (95% CI 1.24–2.14;  $p=0.0005$ ,  $I^2=0\%$ )). The test for subgroup interaction was significant ( $p=0.02$ ). Similar results were found when comparing baseline eosinophils of  $<2\%$  versus  $\geq 2\%$  (RR 1.00 (95% CI 0.82–1.21;  $p=1.00$ ,  $I^2=0\%$ ) versus 1.22 (95% CI 1.04–1.43;  $p=0.01$ ,  $I^2=0\%$ ), respectively). There were no significant differences between the two groups on moderate or severe exacerbation rates when comparing baseline eosinophils of  $<150$  or  $150$ – $299$  cells· $\mu\text{L}^{-1}$  (figure 2) [25, 43].

*Conclusions and research needs*

ICS withdrawal does not increase exacerbation frequency or result in clinically important changes in symptoms or lung function. The evidence is limited due to the small number of studies that met the inclusion criteria, but supports the safety of ICS withdrawal in appropriate patients. This is supported by prior meta-analyses which used broader inclusion criteria including studies that withdrew patients to placebo or SABDs or included studies of shorter duration [27, 28].

Subgroup data for baseline eosinophil counts suggest an important effect on exacerbations, which is reflected in the recommendations. There were insufficient data to perform meaningful subgroup analyses on the other pre-specified subgroups of interest, particularly past history of exacerbations and baseline  $\text{FEV}_1$ .

The studies used a single eosinophil count at baseline and the evidence suggests that this is sufficient to guide withdrawal [44]. Pragmatically, the panel acknowledges that multiple historical eosinophil counts may be available and if several of them, measured during clinical stability, are  $<300$  cells· $\mu\text{L}^{-1}$  this would increase confidence in ICS withdrawal.

Patients in the majority of the trials were infrequent exacerbators (one or less exacerbations in the previous 12 months) apart from the COSMIC study, and both the evidence for ICS use in patients with frequent

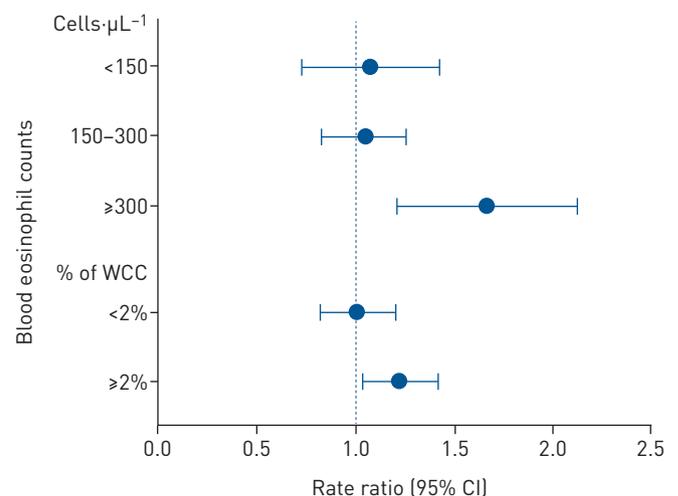


FIGURE 2 Frequency of moderate and severe exacerbations after inhaled corticosteroid (ICS) withdrawal stratified by baseline blood eosinophil counts. WCC: white cell count. Statistically significant increased exacerbation frequency is observed in patients with blood eosinophil counts  $>300$  cells· $\mu\text{L}^{-1}$  or  $\geq 2\%$  of total WCC.

exacerbations and the somewhat worse outcomes for patients in the COSMIC study support only attempting ICS withdrawal in patients with less than two exacerbations per year [21].

Our analysis was not designed to answer whether patients withdrawing from ICS should receive a single or dual LABD treatment. Most studies suggest superiority of dual LABD therapies for end-points of lung function and symptoms, and so the practice of most panel members would be to use dual LABD therapy [45–48].

Future studies should therefore prospectively test algorithms for ICS discontinuation based on blood eosinophils as well as establish whether ICS withdrawal is feasible or desirable in patients with two or more exacerbations per year. It has been demonstrated that ICS primarily reduce exacerbations requiring corticosteroids, but may increase antibiotic-requiring exacerbations [49], and these endotypes are relatively stable over time [50]. Studies aimed to establish whether exacerbation endotype or other patient characteristics such as lung function may predict response to withdrawal are also needed. Future trials may therefore establish whether the requirement for corticosteroids at exacerbation, the presence of eosinophilic exacerbations or the lung microbiome may predict response to ICS withdrawal [50, 51].

### Values and preferences

There is likely to be uncertainty and variability in interpretation of the magnitude of effects. The guideline panel experience is that some clinicians and some patients interpret small changes in exacerbations, SGRQ or FEV<sub>1</sub> as important while others may not regard them as clinically significant [40]. Likewise, patient feedback was that the majority of patients would give high value to exacerbations and symptoms, with low value given the lung function changes in the absence of any impact on symptoms. This is consistent with the systematic review performed by ZHANG *et al.* [52], which rated exacerbations and hospital admissions due to exacerbations as the most important end-points for patients. The personal experience of patients was that most patients would accept ICS withdrawal where this was appropriate. Patients consider it important to avoid withdrawal if this can result in harm and so the availability of a biomarker (blood eosinophils) that could identify patients most likely to benefit from withdrawal was regarded as highly valuable.

### Discussion

ICS are widely used in the treatment of patients with COPD [53, 54]. The availability of combined LABDs and increasing recognition of the potential adverse effects of ICS treatment has led to a gradual re-evaluation of their role [1, 55]. The most recent GOLD document separates initial and ongoing pharmacotherapy for COPD, and it is notable that LABD therapy, rather than ICS-containing therapies, is recommended as initial therapy for all but a small subgroup of patients [1]. Despite this, there is evidence that up to 70% of patients with COPD without a history of frequent exacerbations receive ICS as their initial therapy, even after coexisting asthma is excluded [3, 56, 57]. This suggests widespread overuse or inappropriate use of ICS. Notably, lung function and symptoms may be improved with dual LABDs compared with an ICS/LABA combination, while there are conflicting data on which is superior for preventing exacerbations [56, 58–61].

It is therefore important to consider whether ICS withdrawal may be appropriate for some individuals who do not require ICS. Barriers to ICS withdrawal are concerns that patients may experience an increase in exacerbations, an increase in symptoms, a worsening of lung function or adrenal insufficiency due to abrupt withdrawal of corticosteroids.

The existing evidence suggests that these concerns are largely unfounded when ICS withdrawal is performed in patients without blood eosinophil counts  $\geq 300$  cells· $\mu\text{L}^{-1}$  and without a history of frequent exacerbations. No significant impact of ICS withdrawal on exacerbation frequency was observed, and the differences in quality of life and lung function over 6–12 months were small and not likely to be clinically relevant. Notably, all studies except WISDOM abruptly withdrew ICS with no reports of sudden deteriorations or adrenal insufficiency, suggesting no requirement for gradual withdrawal.

In contrast, in patients with elevated eosinophil counts ( $\geq 300$  cells· $\mu\text{L}^{-1}$ ) there was a large increase in exacerbation frequency that all clinicians would agree is unacceptable. For this reason, despite being based on only two studies, we make a strong recommendation to maintain ICS treatment in patients with evidence of eosinophilic inflammation. This recommendation is supported by extensive evidence showing that blood eosinophil counts reflect, to some degree, the extent of eosinophilic airway inflammation and predict response to ICS [14, 23, 61–64]. Based on this data, GOLD recently introduced blood eosinophil counts into the decision-making process for ICS initiation. For initial therapy, GOLD recommends the same threshold of 300 eosinophils· $\mu\text{L}^{-1}$  to initiate ICS in patients in group D (more symptomatic, with frequent exacerbations); however, in follow-up GOLD recommends to consider the addition of an ICS to LABD in patients with eosinophil counts  $>100$  cells· $\mu\text{L}^{-1}$  if they had two or more moderate exacerbations or one severe exacerbation, and to avoid ICS in patients with levels below this [1]. This is based on

analysis of recent trials which demonstrate no benefit of ICS/long-acting  $\beta$ -agonist (LABA)/long-acting muscarinic antagonist (LAMA) *versus* LABA/LAMA therapy in patients with eosinophil counts  $<100$  cells- $\mu\text{L}^{-1}$  and evidence of benefit above this level [14, 61]. New initiation of ICS in patients with a history of frequent exacerbations is clearly different to withdrawal of ICS in patients without a history of exacerbations. This was supported by our finding of no increase in exacerbations following withdrawal in patients with eosinophil counts between 150 and 300 cells- $\mu\text{L}^{-1}$ . Notably, although prior studies powered to investigate an effect of ICS on mortality failed to demonstrate statistically significant differences between ICS-containing regimens and LABAs alone [65, 66], recent studies have suggested a potential mortality benefit over 12 months with ICS/LABA/LAMA therapy compared with dual bronchodilator therapy [61, 67]. The potential that ICS withdrawal could have a negative impact on mortality was considered by the panel, but was not considered relevant because the impact of ICS on mortality remains to be clearly established. This effect has only been reported in patients with a history of frequent exacerbations, which is a different population to those being recommended for ICS withdrawal; no trend towards increased mortality was observed in the studies of ICS withdrawal.

We did not observe clear benefits of ICS withdrawal, but this is not surprising as the primary benefits, such as a reduced risk of pneumonia, fractures or other adverse effects, may require  $>12$  months of follow-up. Notably, observational studies do suggest significant reductions in adverse events such as pneumonia following ICS withdrawal [68].

Our recommendations do not apply to patients with asthma, and we do not address in this guideline how to differentiate asthma and COPD [69]. The trials included in our meta-analysis all excluded patients with asthma and so our guideline algorithm begins with a clear instruction to exclude asthma. We identified various algorithms or position documents which also suggest taking into account prior history of pneumonia, mycobacterial disease, bronchiectasis and other comorbidities when considering the appropriateness of ICS [68, 70–75]. There is insufficient evidence to demonstrate if any of these factors modify the outcome after ICS withdrawal, but clinicians may take such factors into account when deciding how to apply our recommendations. Other factors which may be taken into account include the history of prior response to ICS and exacerbation history prior to ICS. The studies did not consider exacerbation frequency prior to

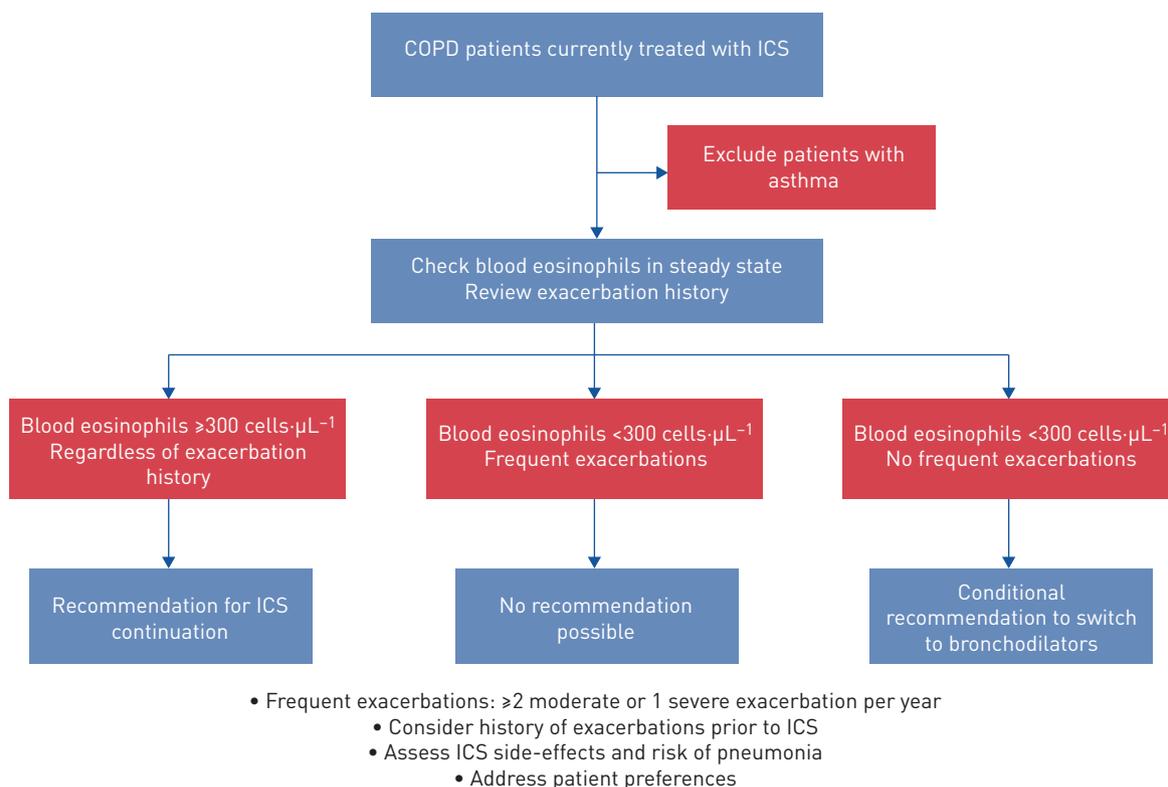


FIGURE 3 Algorithm of the European Respiratory Society guideline on inhaled corticosteroid (ICS) withdrawal in patients with chronic obstructive pulmonary disease (COPD). Note that systemic corticosteroids suppress blood eosinophil counts and so values taken during or after a recent course of oral corticosteroids should not be used.

commencing ICS therapy. The conditional recommendation in this guideline means that clinicians should make a judgement taking into account the views of patients and their individual benefit *versus* risk. A patient with an eosinophil count  $<150$  cells- $\mu\text{L}^{-1}$  and no history of exacerbations with no objective benefit from ICS would be a clear candidate for ICS withdrawal. A patient who had more than two exacerbations per year prior to starting ICS therapy and an eosinophil count between 150 and 300 cells- $\mu\text{L}^{-1}$ , who has objectively and subjectively benefited from ICS, may choose to withdraw ICS or may choose not to withdraw ICS. Guidelines should only be used alongside clinical judgement. Indeed, although we make a strong recommendation to avoid ICS withdrawal in patients with elevated eosinophil counts, observational studies suggest that in clinical practice, carefully selected patients with eosinophil counts  $\geq 300$  cells- $\mu\text{L}^{-1}$  do sometimes withdraw from ICS therapy without a significant increase in exacerbations [76].

In conclusion, we present ERS guidance on the withdrawal of ICS in COPD. The guideline recommendations and associated considerations are summarised in an algorithm in figure 3.

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