

Online supplement to

Withdrawal of Inhaled Corticosteroids in Chronic Obstructive Pulmonary Disease: A European Respiratory Society Guideline

Methods

Search Strategy

We conducted a systematic review and meta-analysis of studies according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations to determine if ICS can be withdrawn safely in patients with chronic obstructive pulmonary disease (COPD). The panel agreed upon the inclusion and exclusion criteria. Studies included were randomised controlled trials that compared the continuation of inhaled corticosteroids (ICS) and ICS withdrawal in outpatients with stable COPD. COPD was defined as per the Global Initiative of Chronic Obstructive Pulmonary Disease. The panel determined that for inclusion in the meta-analysis the ICS withdrawal groups had to be prescribed an alternative long-acting bronchodilator therapy, which is the current standard of care. The follow up period for study inclusion was a minimum of six months. Studies were excluded if the ICS withdrawal group was transitioned to placebo or short-acting bronchodilator therapy only.

One author (IFL) searched for papers published from the inception of the database to May 2019 using Pubmed (Medline), CINAHL and EMBASE. No limits were placed on the database searches. Studies searched were not limited by language and the full-text was sourced if necessary via interlibrary loans. Searches were also supplemented by reviewing the reference lists of the publications and review articles. Additional data were sourced from supplementary material and post-hoc analyses.

The search terms used were as follows:

Pubmed

1 (((("copd") OR "coad") AND ("inhaled corticosteroid" OR "inhaled glucocorticoid") AND withdraw*) AND exacerbation)
 2 COPD and (inhaled corticosteroid or inhaled glucocorticoid) and randomised controlled trial
 3 (pulmonary disease, chronic obstructive) AND (inhalers) AND (glucocorticoids OR triple therapy OR LAMA OR LABA OR beta agonist OR anticholinergic OR muscarinic antagonist) AND (withdrawal OR de-escalation OR switch OR discontinuation)

CINAHL

1 ((MH "Pulmonary Disease, Chronic Obstructive+") AND (((MH "Administration, Inhalation") OR "inhaled corticosteroid") OR ("inhaled glucocorticoid") OR "ICS") AND ("withdraw*" OR "cease" OR "cessation" OR "de-escalat*" OR "switch" OR "discontin*" OR "chang*"))

EMBASE

1 ((COPD or chronic obstructive pulmonary disease or chronic obstructive lung disease or chronic obstructive airways disease) and (ICS or inhaled corticosteroid or inhaled glucocorticoid) and (LAMA or LABA or triple therapy or dual therapy or bronchodilator or long acting beta agonist or anti-muscarinic or anticholinergic) and (withdraw* or de-escalat* or switch* or chang* or discontinu* or cease or cessation)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

Outcomes

The panel determined the outcomes of interest for the meta-analysis, which were rated as either critical or important. The outcomes that were rated as critical were exacerbation rates, respiratory hospitalisations, quality of life measures, adverse effects and pneumonia. The remainder of the outcomes were rated as important and included type of exacerbations, health care resource utilisation, all-cause hospitalisation, FEV₁, use of reliever medication, dyspnoea, exercise capacity and all-cause mortality. Pre-specified subgroup analyses of interest were

eosinophil levels, prior exacerbation history and baseline FEV₁. We also sought data on history of asthma, dosage of ICS, duration of ICS prior to withdrawal, the period of time over which ICS were withdrawn (abrupt vs stepwise or gradual) and prior type of therapy (triple therapy, ICS/long-acting beta agonist (LABA) or unspecified).

Data analysis

Studies were selected for inclusion via consensus decision of three authors (IFL, JDC and MM) after review of the full text and the selection was approved by the full panel. Data collection was performed independently by two authors (IFL and JDC) in a blinded fashion for all outcomes of interest. We collected the data onto a predesigned spreadsheet for consistency and the data were checked by two other authors (MM and DR). Exacerbation rates were determined via three measures (exacerbation frequency, time to first exacerbation and number of patients experiencing at least one exacerbation). Respiratory hospitalisations were taken from the rates of severe exacerbations since severe exacerbations were defined as those requiring hospitalisation. Quality of life measures used were the St Georges Respiratory Questionnaire (SGRQ) and the Clinical COPD Questionnaire (CCQ). Symptoms were measured via dyspnoea scores and the Transition Dyspnoea Index (TDI).

Statistical analysis

We performed the meta-analysis for all critical outcomes and for subgroups where there were sufficient data using Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

We collected the number of patients who had each outcome and the denominator for categorical outcomes and the sample size and mean or median depending on how the data were presented in the studies for continuous outcomes. We collected the number of patients in each group, effect estimate and confidence intervals for effect estimates. We selected the intention-to-treat datasets when more than one set of results were reported. Significance for p values was set at a threshold of 0.05.

For dichotomous outcomes, data are presented as pooled risk ratios or odds ratios (ORs) and 95% CIs. Continuous variables are presented as mean differences with 95% CI. Effect estimates of time to event data or rate ratios were pooled by the inverse of their variance and are presented as pooled effect estimates (hazard ratios [HRs] or rate ratios) with corresponding 95% CIs. All analyses used random effects meta-analysis using the method of DerSimonian and Laird because of the heterogeneity of study designs. The threshold for significance for p values was 0.05.

The I² statistic was used to describe heterogeneity between studies. This represents the percentage of variation across studies due to heterogeneity rather than chance, and was calculated as previously described. Low heterogeneity was less than 30%, moderate heterogeneity was 30-60% and high heterogeneity was greater than 60%.

The subgroup analysis was performed for eosinophil levels at baseline, which was the only pre-specified subgroup with sufficient data. The data were analysed as effect estimates and are presented as rate ratios with 95% confidence intervals.

The risk of bias and evidence grading were assessed by four authors (IFL, JDC, MM and DR) using GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from grade.pro.org.

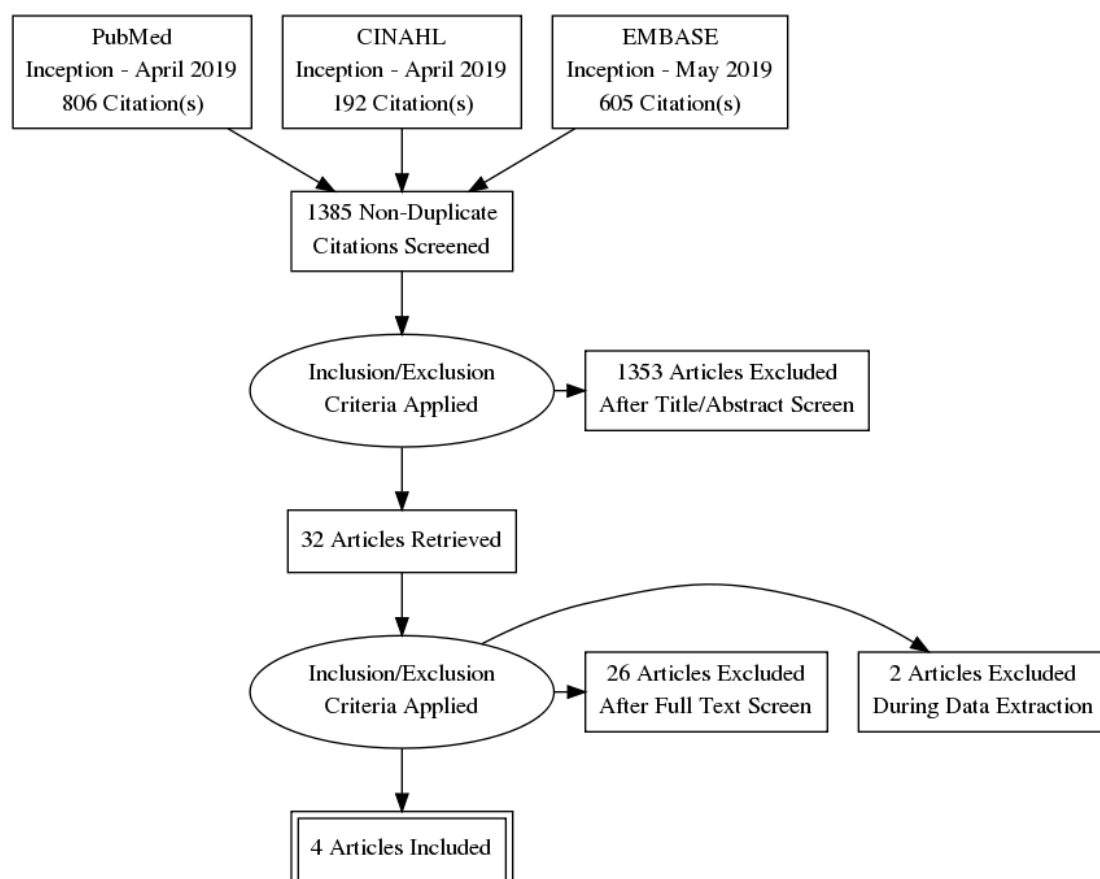
The Evidence to Decision framework was completed at a meeting attended by the majority of the panel, which included patient representatives.

Results (extended)

Summary of the evidence

The database searches revealed a total of 1603 of papers and once duplicates were removed, the total was 1385. Once the inclusion and exclusion criteria were applied by the authors, four studies were included in the meta-

analysis: COSMIC (Wouters et al, Thorax 2005), WISDOM (Magnussen et al, NEJM 2014), INSTEAD (Rossi et al, ERJ 2014) and SUNSET (Chapman et al, AJRCCM 2018).



The total number of patients in the four trials was 4492. Patients were included in all four studies if they were over the age of 40 years with a history COPD defined as having had a smoking history of at least 10 pack years and a FEV₁ to FVC ratio less than 0.70 (with the exception of the COSMIC study (0.88 or 0.89 predicted according to gender)). Patients with moderate or severe COPD and stable disease status (ie no exacerbations) during the screening or run-in periods were included. Patients with other respiratory disorders or on long-term oxygen therapy were excluded. The majority of patients recruited were not frequent exacerbators (INSTEAD, SUNSET, WISDOM) 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.

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 and fluticasone propionate (SFC) 50/500 micrograms twice daily. The groups were then assigned to either continuing SFC or switch to salmeterol 50 micrograms twice daily for one year. Patients recruited to the INSTEAD trial were included if they had received treatment with SFC 50/500 micrograms for at least three 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 micrograms once daily for 26 weeks. At the time of screening for the WISDOM trial patients were in dual bronchodilator therapy and were given triple therapy (SFC 50/500 micrograms twice daily and tiotropium 18 micrograms once daily) for a run-in period of six weeks. They were then randomised to either continue triple therapy or have the fluticasone dose weaned in a stepwise manner over the first 12 weeks and continued on the assigned therapy until 12 months of follow up. The SUNSET trial recruited patients who had been on triple therapy for at least six months prior to screening. Patients were all given SFC 50/500 micrograms twice daily with tiotropium 18 micrograms daily during a four-week run-in period before being randomised to either continue triple therapy or switch to indacaterol/glycopyrronium 110/50 micrograms once daily for 26 weeks. Patients were given placebo inhalers to conceal the treatment protocol to which they had been assigned.

Meta-analyses were performed on the outcomes rated as critical and the subgroup analysis on baseline eosinophils. Other results are presented descriptively.

Critical outcomes

Exacerbation endpoints

Exacerbation endpoints reported in the included studies were exacerbation frequency, time to first exacerbation and number of individuals with at least one exacerbation. All studies reported moderate and severe exacerbations together as a single endpoint. However, one study (INSTEAD) reported mild, moderate and severe together and did not specify moderate and severe separately for the frequency endpoint. As the mild event rate was low in this study the data were pooled with a sensitivity analysis performed excluding this study. Moderate exacerbations were defined as requiring therapy such as antibiotics and/or systemic corticosteroids and severe exacerbations were defined as requiring hospitalisation.

The meta-analysis found that inhaled corticosteroid withdrawal was not associated with an increased frequency of exacerbations. The effect estimate for the endpoint of frequency of moderate or severe exacerbations was rate ratio (RR) 1.05 (95% CI 0.97 to 1.13, $p=0.23$, $I^2=0\%$) across all four studies at the end of treatment (6 or 12 months) with no significant difference between ICS withdrawal and continuation. Time to first moderate or severe exacerbations was measured in three studies (WISDOM/INSTEAD/SUNSET) with no clear effect of inhaled corticosteroid withdrawal, hazard ratio (HR) 1.04 (95% CI 0.94 to 1.16, $p=0.42$, $I^2=2\%$). For the effect estimate of the number of patients experiencing at least one moderate or severe exacerbation, which was reported in two studies (COSMIC/INSTEAD), the effect was odds ratio (OR) 0.84 (95% CI 0.63 to 1.14, $p=0.26$, $I^2=0\%$).

The annual moderate or severe exacerbation rates were 1.6 per patient-year in the ICS withdrawal group and 1.3 per patient-year in the ICS continuation group in the COSMIC study. In the WISDOM study, the adjusted event rate was 0.95 per patient-year in the ICS withdrawal group and 0.91 per patient-year in the ICS continuation group. The rate of all exacerbations per year was 0.57 vs 0.67 in the ICS withdrawal and continuation groups respectively in the INSTEAD trial. In the SUNSET trial, the annual rate of moderate or severe exacerbations was 0.52 vs 0.48 in the ICS withdrawal and continuation groups respectively.

Respiratory Hospitalisations

Respiratory hospitalization and severe exacerbations were used interchangeably in the studies and therefore in our meta-analysis. In the INSTEAD trial for the endpoints of the number of patients experiencing at least one severe exacerbation, ICS withdrawal resulted in an OR of 0.49 (95% CI 0.04 to 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 trial measured time to first severe exacerbation, which resulted in a HR of 1.20 (95% CI 0.98 to 1.48) for ICS withdrawal. As there are only two studies, we did not provide a pooled effect estimate.

Quality of Life

The St George's Respiratory Questionnaire (SGRQ) was performed in all four studies and the pooled mean difference between the two arms was -0.87 (95% CI -1.72 to -0.02, $p=0.05$, $I^2=21\%$). The COPD Assessment Test (CAT) was not included in any of the studies. The Clinical COPD Questionnaire (CCQ) was used in the COSMIC study and there was a difference of 0.13 (standard error (SE) 0.06), $p=0.041$ between the two groups after 12 months with higher scores indicating worse symptoms in the ICS withdrawal group at all time points during the study, except at the 12 month point.

Adverse effects

The COSMIC study was not included in the meta-analysis as the data were presented as the total number of adverse events rather than number of patients with adverse events. The number of adverse events was similar in both arms in this study: total adverse events 516 vs 529 and treatment related adverse events 25 vs 26, ICS withdrawal vs continuation respectively. There were no statistically significant differences between ICS withdrawal and continuation in the number of patients experiencing adverse events in the pooled analysis of the other three studies, OR 0.94 (95% CI 0.82 to 1.08, $p=0.41$, $I^2=55\%$).

Pneumonia

The rates of pneumonia were not available in the COSMIC study. The other three studies were included in the meta-analysis and the results favoured ICS withdrawal, but were not statistically significant, OR 0.89 (95% CI 0.64 to 1.22,

$p=0.46$, $I^2=0\%$). Absolute numbers of pneumonia events were low with 74/1792 (4.13%) in the ICS withdrawal group and 83/2057 (4.04%) in the ICS continuation group.

Important Outcomes

Types of exacerbations

There were no other results or data presented for specific types of exacerbations other than what has already been described.

Health care resource utilisation

No data were provided on health care resource utilisation in these studies.

All-cause hospitalisations

There were no results for all-cause hospitalisations. Hospitalisations for serious adverse events were similar between the two groups in the WISDOM study, 271/1242 (21.82%) vs 273/1243 (21.96%), ICS withdrawal vs continuation respectively.

FEV₁

In the COSMIC study, there was a significant reduction in pre-dose FEV₁ after the ICS run-in period with an adjusted difference of 4.1 percentage points favouring ICS continuation. The difference between the two arms of the study after 12 months was 50 mL (95% CI 10 to 100 mL, $p=0.022$).

At the end of the ICS withdrawal period at week 18 in the WISDOM study, the adjusted mean reduction in trough FEV₁ from baseline was 38 mL greater in the ICS withdrawal group and remained similar at the end of the study at week 52 with an adjusted mean reduction of 43 mL greater in the ICS withdrawal group.

In INSTEAD, the least squares mean values for trough FEV₁ at week 12 were 1.584 (SE 0.0294) L for ICS withdrawal and 1.593 (SE 0.0300) L for ICS continuation with a difference of -0.009 L (95% CI -0.045 to 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.

At the end of the SUNSET study (day 182), the difference in least squares mean for trough FEV₁ from baseline was -26 mL (95% CI -53 to 1 mL, $p=0.573$). There was a consistently lower mean trough FEV₁ in the ICS withdrawal group compared to the ICS continuation and the results were statistically significant until day 181.

Use of rescue medication

Use of rescue medication was presented differently in each study and no data were available for the WISDOM study. The mean percentage of rescue medication free days in the COSMIC study was 47% (SE 2%) in ICS withdrawal group and 53% (SE 2%) in the continuation group ($p=0.014$). In the INSTEAD trial the percentages of rescue medication free days were 52.8% vs 54.6% ($p=0.505$) in the ICS withdrawal and continuation groups respectively. The mean change in puffs per day of rescue medication were -0.44 vs -0.49 respectively, with a difference of 0.05 (95% CI -0.17 to 0.28, $p=0.650$). In the SUNSET trial the difference in puffs per day between the two arms was 0.177 (95% -0.01 to 0.36) and the difference in rescue medication free days between the two arms was 0.103 (95% CI -3.25 to 3.25).

Dyspnoea

Dyspnoea scores on a scale of 0-4 were measured in the COSMIC study and there was a mean adjusted difference of 0.17 (SE 0.04) after 12 months. The modified Medical Research Council (mMRC) dyspnoea score was used to measure symptoms in the WISDOM study. At 12 months, the withdrawal group had an increase in mMRC score of 0.035 compared to a drop of 0.028 in the ICS continuation group. The Transitional Dyspnoea Index (TDI) was measured in the INSTEAD and SUNSET trials. The difference between the two groups was -0.12 (95% CI -0.71 to 0.48, $p=0.694$) in the total score measured via least squares mean after 26 weeks in the INSTEAD study with 68.7% and 69.4% of participants in the ICS withdrawal and continuation arms respectively achieving the MCID, OR 0.88 (95% CI 0.58 to 1.35, $p=0.56$). The difference between the two groups in the total score at 26 weeks in the SUNSET trial was -0.28 (95% CI -0.63 to 0.06).

Exercise capacity

Exercise capacity was not measured in any of the studies.

All-cause mortality

Overall, all-cause mortality was low in the three studies that reported it and there were no significant differences between the two groups. In the WISDOM study, the ICS withdrawal group had 43/1242 deaths (3.46%) and the ICS continuation group had 38/1243 deaths (3.06%) at the end of the study including the follow up period. At 26 weeks there were no deaths in the ICS withdrawal group and 2/288 deaths (0.69%) in the continuation group in the INSTEAD study. In the SUNSET study, the deaths were 4/527 (0.76%) and 5/526 (0.95%) in the ICS withdrawal and continuation groups respectively. The data were not pooled due to the low number of events.

Subgroup Analyses

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

In patients with eosinophil counts $<300 \text{ cells} \cdot \mu\text{L}^{-1}$ there was no effect of ICS withdrawal of exacerbation rate, RR 1.03 (95% CI 0.90 to 1.18, $p=0.71$, $I^2=0\%$) but there was a significant increase in exacerbations in patients with eosinophil counts $\geq 300 \text{ cells} \cdot \mu\text{L}^{-1}$, RR 1.63 (95% CI 1.24 to 2.14, $p=0.0005$, $I^2=0\%$). Similar results were found when comparing baseline eosinophils of $<2\%$ vs $\geq 2\%$, RR 1.00 (95% CI 0.82 to 1.21, $p=1.00$, $I^2=0\%$) vs RR 1.22 (95% CI 1.04 to 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 $<150 \text{ cells} \cdot \mu\text{L}^{-1}$ or $150\text{--}299 \text{ cells} \cdot \mu\text{L}^{-1}$. The test for subgroup interaction was significant ($p=0.02$).

GRADE Evidence Tables

Author(s): Irena Laska, Marc Miravittles, James Chalmers

Date:

Question: Withdrawal of inhaled corticosteroids compared to continuation of inhaled corticosteroids for COPD

Setting: Outpatients with COPD

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	withdrawal of inhaled corticosteroids	continuation of inhaled corticosteroids	Relative (95% CI)	Absolute (95% CI)		
Frequency of moderate or severe exacerbations												
4 ^{1,2,3,4}	randomised trials	not serious	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	-/0	-/0	Rate ratio 1.05 (0.98 to 1.12)	-- per 1000 patient(s) per years (from -- to --)	HIGH	CRITICAL
Number of patients with at least one moderate or severe exacerbation												
2 ^{2,4}	randomised trials	not serious	not serious	serious ^a	not serious	none	157/477 (32.9%)	174/477 (36.5%)	OR 0.84 (0.63 to 1.14)	39 fewer per 1,000 (from 99 fewer to 31 more)	MODERATE	CRITICAL
Time to first moderate or severe exacerbation												
3 ^{1,2,3}	randomised trials	not serious	not serious	not serious	not serious	none	-/0	-/0	HR 1.04 (0.94 to 1.16)	1 fewer per 1,000 (from 1 fewer to 1 fewer)	HIGH	CRITICAL
Number of patients with at least one severe exacerbation												
1 ²	randomised trials	serious ^b	not serious	serious ^c	not serious	none	1/293 (0.3%)	2/288 (0.7%)	OR 0.49 (0.04 to 5.43)	4 fewer per 1,000 (from 7 fewer to 30 more)	LOW	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	withdrawal of inhaled corticosteroids	continuation of inhaled corticosteroids	Relative (95% CI)	Absolute (95% CI)		

SGRQ

4 ^{1,2,3,4}	randomised trials	not serious	not serious	not serious	not serious	none	0	0	-	MD 0.87 lower (1.72 lower to 0.02 lower)	HIGH	CRITICAL
----------------------	-------------------	-------------	-------------	-------------	-------------	------	---	---	---	------------------------------------------	------	----------

Adverse events

3 ^{1,2,3}	randomised trials	not serious	not serious	not serious	not serious	none	1447/2062 (70.2%)	1468/2057 (71.4%)	OR 0.94 (0.82 to 1.08)	13 fewer per 1,000 (from 42 fewer to 15 more)	HIGH	CRITICAL
--------------------	-------------------	-------------	-------------	-------------	-------------	------	-------------------	-------------------	------------------------	-----------------------------------------------	------	----------

Pneumonia

3 ^{1,2,3}	randomised trials	serious ^d	not serious	not serious	not serious	none	74/2062 (3.6%)	83/2057 (4.0%)	OR 0.89 (0.64 to 1.22)	4 fewer per 1,000 (from 14 fewer to 8 more)	MODERATE	CRITICAL
--------------------	-------------------	----------------------	-------------	-------------	-------------	------	----------------	----------------	------------------------	---------------------------------------------	----------	----------

Baseline eosinophils <2% on rate of moderate or severe exacerbations

2 ^{1,3}	randomised trials	serious ^e	not serious	not serious	serious ^f	none	-/0	-/0	Rate ratio 1.00 (0.82 to 1.21)	-- per 1000 patient(s) per years (from -- to -)	LOW	CRITICAL
------------------	-------------------	----------------------	-------------	-------------	----------------------	------	-----	-----	--------------------------------	-------------------------------------------------	-----	----------

Baseline eosinophils >2% on rate of moderate or severe exacerbations

2 ^{1,3}	randomised trials	serious ^e	not serious	not serious	serious ^g	none	-/0	-/0	Rate ratio 1.22 (1.04 to 1.43)	-- per 1000 patient(s) per years (from -- to -)	LOW	CRITICAL
------------------	-------------------	----------------------	-------------	-------------	----------------------	------	-----	-----	--------------------------------	-------------------------------------------------	-----	----------

Baseline eosinophils <150/microlitre on rate of moderate or severe exacerbations

2 ^{1,3}	randomised trials	serious ^e	not serious	not serious	serious ^f	none	-/0	-/0	Rate ratio 1.11 (0.93 to 1.31)	-- per 1000 patient(s) per years (from -- to -)	LOW	CRITICAL
------------------	-------------------	----------------------	-------------	-------------	----------------------	------	-----	-----	--------------------------------	-------------------------------------------------	-----	----------

Baseline eosinophils 150-299/microlitre on rate of moderate or severe exacerbations

2 ^{1,3}	randomised trials	serious ^e	not serious	not serious	serious ^f	none	-/0	-/0	Rate ratio 1.03 (0.84 to 1.27)	-- per 1000 patient(s) per years (from -- to -)	LOW	CRITICAL
------------------	-------------------	----------------------	-------------	-------------	----------------------	------	-----	-----	--------------------------------	-------------------------------------------------	-----	----------

Baseline eosinophils <300/microlitre on rate of moderate or severe exacerbations

2 ^{1,3}	randomised trials	serious ^e	not serious	not serious	not serious	none	-/0	-/0	Rate ratio 1.03 (0.90 to 1.18)	-- per 1000 patient(s) per years (from -- to -)	MODERATE	CRITICAL
------------------	-------------------	----------------------	-------------	-------------	-------------	------	-----	-----	--------------------------------	-------------------------------------------------	----------	----------

Baseline eosinophils >300/microlitre on rate of moderate or severe exacerbations

2 ^{1,3}	randomised trials	serious ^e	not serious	not serious	not serious	none	-/0	-/0	Rate ratio 1.63 (1.24 to 2.14)	-- per 1000 patient(s) per years (from -- to -)	MODERATE	CRITICAL
------------------	-------------------	----------------------	-------------	-------------	-------------	------	-----	-----	--------------------------------	-------------------------------------------------	----------	----------

CI: Confidence interval; OR: Odds ratio; HR: Hazard Ratio; MD: Mean difference

Explanations

a. Step down was to a single bronchodilator in both studies. It was difficult to extract data from the papers. The two larger studies did not report this end point.

b. The other three studies did not report this end point.

c. Step down was to a single bronchodilator.

d. Pneumonia was a rare event. The duration of the studies was too short or the studies had too few patient numbers to detect an effect.

e. Impact of baseline eosinophil levels on exacerbations in the WISDOM study was determined in a post-hoc analysis. Neither study stratified randomisation based on eosinophil levels at baseline.

f. The MCID for exacerbations in COPD is suggested to be 20%. This is exceeded by these data and may represent a clinically relevant difference.

g. Confidence intervals include only a 4% increase in exacerbations which would not be clinically meaningful.

References

1. Helgo Magnussen, Henrik Watz, Anne Kirsten, Marc Decramer, Ronald Dahl, Peter M. A. Calverley, Lesley Towse, Helen Finnigan, Kay Tetzlaff, Bernd Disse. Stepwise withdrawal of inhaled corticosteroids in COPD patients receiving dual bronchodilation: WISDOM study design and rationale. *Respiratory Medicine*; 2014.
2. Andrea Rossi, Thys van der Molen, Ricardo del Olmo, Alberto Papi, Luis Wehbe, Matthew Quinn, Chengxing Lu, David Young, Ray Cameron, Enrica Bucchioni, Pablo Altman. INSTEAD: a randomised switch trial of indacaterol versus salmeterol/fluticasone in moderate COPD. *European Respiratory Journal*; 2014.
3. Kenneth R. Chapman, John R. Hurst, Stefan-Marian Frent, Michael Larbig, Robert Fogel, Tadhg Guerin, Donald Banerji, Francesco Patalano, Pankaj Goyal, Pascal Pfister, Konstantinos Kostikas, Jadwiga A. Wedzicha. Long-Term Triple Therapy De-escalation to Indacaterol/ Glycopyrronium in Patients with Chronic Obstructive Pulmonary Disease (SUNSET): A Randomized, Double-Blind, Triple-Dummy Clinical Trial. *American Journal of Respiratory and Critical Care Medicine*; 2018.
4. E F M Wouters, D S Postma, B Bokkens, WC J Hop, J Prins, A F Kuipers, H R Pasma, C A J Hensing, E C Creutzberg, for the COSMIC (COPD and Seretide: a Multi-Center Intervention and Characterization) Study Group. Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial. *Thorax*; 2005.

Final evidence to decision framework

Domain	Judgement	Research evidence Additional considerations
DESIRABLE EFFECTS	<p>How substantial are the desirable anticipated effects?</p> <ul style="list-style-type: none"> ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know 	<p>Research evidence did not detect clinically meaningful differences in reduction of adverse events related to inhaled corticosteroids (ICS) withdrawal; however, it is expected that ICS withdrawal reduces steroid-related adverse events over the long-term in addition to a reduced medication burden, and better use of healthcare resources.</p> <p>It is acknowledged that some patients will not experience a benefit from ICS withdrawal while other patients may notice a substantial benefit.</p>
UNDESIRABLE EFFECTS	<p>How substantial are the undesirable anticipated effects?</p> <ul style="list-style-type: none"> ○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know 	<p>Theoretically inhaled corticosteroid withdrawal could increase exacerbations, reduce lung function and reduce quality of life. In our analysis only quality of life was significantly reduced and this was substantially below the MCID.</p>
	<p>What is the overall certainty of the evidence of effects?</p> <ul style="list-style-type: none"> ○ Very low ○ Low ● Moderate ○ High 	<p>For the majority of endpoints the evidence is relatively consistent with low imprecision for exacerbation frequency for example, there are limited data available for analysis on endpoints such as FEV₁, hospitalizations and the studies are of relatively short duration.</p> <p>Overall certainty of the subgroup effects for eosinophils is low as</p>

	<ul style="list-style-type: none"> ○ No included studies 	<p>there were even fewer studies and only one with eosinophil analysis as a pre-specified endpoint.</p>
VALUES	<p>Is there important uncertainty about or variability in how much people value the main outcomes?</p> <ul style="list-style-type: none"> ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability ○ No known undesirable outcomes 	<p>No research evidence included. The judgement reflects the guideline panel considerations.</p> <p>The analysis of important/critical outcomes showed a very high level of agreement on the importance of the selected outcomes. There is likely to be uncertainty and variability in interpretation of magnitude of effects. The guideline panel experience is that some clinicians and some patients interpret small changes in exacerbations, SGRQ or FEV₁ as important while others may not regard them as clinically significant.</p> <p>The patient perspective from the European Lung Foundation patient representative 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.</p>
BALANCE OF EFFECTS	<p>Does the balance between desirable and undesirable effects favour the intervention or the alternative?</p> <ul style="list-style-type: none"> ○ Favours the alternative ○ Probably favours the alternative ○ Does not favour either the intervention or the alternative ● Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know 	<p>The research evidence reveals that there is little difference in outcomes between either withdrawing or continuing ICS. There are uncertainties about the balance over the long-term due to the relatively short duration of studies.</p> <p>Based on the apparent lack of detrimental effects on exacerbations with the ICS withdrawal, the potential reduction of adverse events and treatment burden, the guideline panel considered that the overall balance favours the withdrawal of ICS in appropriate patients.</p>
RESOURCES REQUIRED	<p>How large are the resource requirements (costs)?</p> <ul style="list-style-type: none"> ○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies 	<p>No research evidence included. The judgement reflects the guideline panel considerations.</p> <p>There are likely to be small cost savings associated with reduced ICS prescribing, but as these medications are not expensive in most healthcare systems, the savings are likely to be modest and patients will still be prescribed one or more inhalers.</p>

	<input type="radio"/> Don't know	
EQUITY	<p>What would be the impact on health equity?</p> <input type="radio"/> Reduced <input type="radio"/> Probably reduced <input checked="" type="radio"/> Probably no impact <input type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> Don't know	<p>No research evidence included. The judgement reflects the guideline panel considerations. We considered there would likely be no impact on health equity.</p>
ACCEPTABILITY	<p>Is the intervention acceptable to key stakeholders?</p> <input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	<p>No research evidence included. The judgement reflects the guideline panel considerations.</p> <p>The majority of clinicians accept that unnecessary or inappropriate used medications should be withdrawn where they are not providing clinical benefits. The intervention is therefore likely to be acceptable among some but not all healthcare professionals.</p> <p>Feedback was provided by the European Lung Foundation patient advisor. The patients personal experience was that most patients would accept inhaled corticosteroid withdrawal where this was appropriate. Patients consider it important to avoid withdrawal in patients where this can result in harm and so they emphasise the importance of the subgroup data on blood eosinophils from a patients perspective.</p>
FEASIBILITY	<p>Is the intervention feasible to implement?</p> <input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	<p>No research evidence included. The judgement reflects the guideline panel considerations.</p> <p>Yes. Prescription of inhaled medications is already standard of practice and monitoring can be done in standard healthcare settings.</p>

Should inhaled corticosteroids be withdrawn in patients with COPD and a low frequency of exacerbations?					
TYPE OF RECOMMENDATION	Strong recommendation	Conditional recommendation	Conditional recommendation	Conditional recommendation	Strong recommendation

	n against the intervention ○	n against the intervention ○	n for either the intervention or the alternative ○	n for the intervention ●	n for the intervention ○
RECOMMENDATION	<p>1) For patients with COPD without a history of frequent exacerbations consider ICS withdrawal (conditional recommendation, moderate quality of evidence) and measure blood eosinophil count to help decision-making.</p> <p>2) We recommend <u>not</u> to withdraw ICS in patients who have a blood eosinophil count ≥ 300 eosinophils·μL^{-1}, with or without a history of frequent exacerbations (strong recommendation, moderate quality of evidence).</p> <p>3) For patients with COPD and a history of frequent exacerbations but < 300 eosinophils·μL^{-1}, no recommendation can be formulated</p> <p>4) If ICS are withdrawn, patients should be treated with one or two long-acting bronchodilators (strong recommendation, moderate quality of evidence).</p> <p>Note that patients without a history of frequent exacerbations are those with no more than one moderate exacerbation in the previous year.</p>				
JUSTIFICATION	<p>This recommendation is based on the evidence identified which showed no increase in exacerbations or clinically significant deterioration in symptoms following inhaled corticosteroid withdrawal.</p> <p>We have limited the recommendation to patients with infrequent exacerbations as patients in the majority of the trials were infrequent exacerbators (0-1 in the previous 12 months) apart from the COSMIC study. Also it has been suggested in well-designed, larger and longer trials assessing efficacy of ICS and inhaled bronchodilators that outcomes are superior with ICS use in frequent exacerbators (≥ 2 per year).</p> <p>We recommended stepping down to bronchodilator therapy as the two larger trials (WISDOM and SUNSET) stepped down to dual therapy and included patients with moderate to severe COPD, where dual therapy has been proven to be more efficacious than single bronchodilator therapy.</p> <p>The recommendations regarding eosinophil subgroups are based on the evidence presented in “subgroup considerations” below.</p>				
SUBGROUP CONSIDERATIONS	<p>Subgroup data for baseline eosinophil counts suggest an important subgroup effect on exacerbations, which is reflected in the recommendations above. There were insufficient data to perform meaningful subgroup analyses on the other pre-specified subgroups of interest, particularly past history of exacerbations and baseline FEV₁.</p> <p>The studies used a single eosinophil count at baseline and the evidence suggests that this is sufficient to guide withdrawal. Pragmatically the panel acknowledges that multiple historic eosinophil counts may be available in daily clinical practice. Where multiple eosinophil counts measured during clinical stability are available and below 300 cells·μL^{-1}, this would increase confidence in ICS withdrawal.</p>				
IMPLEMENTATION CONSIDERATIONS	<p>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</p>				

	withdrawn in the majority of cases.
MONITORING AND EVALUATION	Some patients may deteriorate following any change in treatment, including ICS withdrawal. Therefore monitoring of exacerbation frequency, symptoms and lung function is recommended.
RESEARCH PRIORITIES	Further trials with larger numbers of patients that include subgroup analyses, such as those mentioned above, are required.