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Withdrawal of Inhaled Corticosteroids from Patients with COPD; Effect on Exacerbation Frequency and Lung Function: A Systematic Review

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Background: Inhaled corticosteroid (ICS) therapy has been demonstrated to reduce the risk of COPD exacerbations. It should only be prescribed to COPD patients who are not adequately controlled by dual long-acting bronchodilator therapy and who have ≥2 exacerbations per year and a blood eosinophil count ≥300cells/μL. ICS therapy is widely prescribed outside guidelines to COPD patients, making ICS withdrawal an important consideration. This systematic review aims to provide an up-to-date analysis of the effect of ICS withdrawal on exacerbation frequency, change in lung function (FEV_1) and to determine the proportion of COPD patients who resume ICS therapy following withdrawal.

Methods: Randomised controlled trials (RCTs) and observational studies which compared ICS withdrawal with ICS continuation treatment were included. Cochrane Central, Web of Science, CINHAL, Embase and OVID Medline were searched. Risk of bias was assessed using the Cochrane RoB2 tool and the Newcastle-Ottawa Scale. Quality assessment of RCTs was conducted using GRADE. Meta-analysis of post-hoc analyses of RCTs of ICS withdrawal, stratified by blood eosinophil count (BEC), was undertaken.

Results: Ten RCTs (6642 patients randomised) and 6 observational studies (160,029 patients) were included in the results. When ICS was withdrawn and long-acting bronchodilator therapy was maintained, there was no consistent difference in exacerbation frequency or lung function change between the ICS withdrawal and continuation trial arms. The evidence for these effects was of moderate quality. There was insufficient evidence to draw a firm conclusion on the proportion of patients who resumed ICS therapy following withdrawal (estimated range 12–93% of the participants).

Discussion: Withdrawal of ICS therapy from patients with COPD is safe and feasible but should be accompanied by maintenance of bronchodilation therapy for optimal outcomes.

Keywords: COPD, inhaled corticosteroid, drug withdrawal, exacerbations, randomised controlled trials, observational studies

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a progressive chronic disease characterized by irreversible, fixed airways obstruction, progressive destruction of lung parenchyma and airways inflammation.[1] Mucus hypersecretion and narrowing of the airways[2] contribute to symptoms including excessive sputum production, dyspnoea and chronic cough[3] punctuated by episodes of acute worsening of symptoms known as exacerbations.[4] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 guidelines recommend that the mainstay of treatment for COPD patients includes long-acting muscarinic antagonists (LAMA) and long-acting beta agonists (LABA).[5,6] These long-acting bronchodilators can be prescribed alone, as a dual therapy with LABA/LAMA, or in combination with inhaled corticosteroids (ICS) as a triple therapy as LABA/LAMA/ICS to relieve symptoms and prevent exacerbations of COPD.[7]

In accordance with the GOLD guidelines, only symptomatic COPD patients with a blood eosinophil count (BEC) of ≥300 cells/μL and with ≥2 exacerbations per year, who are inadequately controlled by LABA/LAMA therapy, should be given ICS therapy.[6,8] Patients with raised BECs have a better response to ICS therapy than patients with low BECs.[9,10] Despite this guidance, many patients with a diagnosis of COPD, without a history of frequent exacerbations and mild or

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moderate airflow limitation continue to be prescribed ICS therapy, in spite of the lack of evidence of efficacy.[11] Up to 70% of newly diagnosed COPD patients are prescribed ICS therapy from initiation of inhaled treatment.[12] Overprescription of ICS therapy poses a burden for patients and the healthcare system as their use increases the likelihood of adverse effects including glaucoma, cataracts, pneumonia and osteoporosis.[13]

Despite the increasing evidence for the safety and feasibility of ICS withdrawal and its prominence in clinical guidelines,[9,12,14] a number of recent studies suggest that the intervention may lead to a deterioration in clinical outcomes.[15,16] In addition, little is known of the participants who fail a trial of withdrawal. The primary aim of this systematic review was to examine the effect of ICS withdrawal on the exacerbation frequency and change in lung function (FEV_1) of COPD patients. The secondary aim was to determine the prevalence of resumption of ICS therapy among COPD patients who had undergone ICS withdrawal. The review seeks to assist in the identification of COPD patients eligible for a trial of ICS withdrawal and to improve patient safety in the withdrawal process.

Methods

This systematic review aimed to evaluate the effect of ICS withdrawal on the exacerbation frequency and lung function of COPD patients and to determine the proportion of patients who resumed ICS therapy following withdrawal. The search strategy, structure, and conduct of this review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist.[17]

Eligibility Criteria

Randomised controlled trials (RCTs) and non-randomised observational studies were included in this review. The RCTs of ICS withdrawal randomised patients into ICS withdrawal and ICS continuation arms. Included studies reported one or more of the outcomes of this review (Table 1). Exacerbations were defined as moderate where antibiotics and/or oral corticosteroids were prescribed for the treatment of COPD symptoms, and severe where hospital admission was required for the treatment of COPD symptoms.[18] Included inhaled corticosteroids were mometasone, ciclesonide, flunisolide, beclometasone, budesonide, triamcinolone and fluticasone. Exclusion criteria were all review articles, commentary articles or editorials. Studies that were not in English were also excluded. A full table of inclusion/exclusion criteria can be found in the Supplementary File and Supplementary Table S1.

Search Strategy

The PICO (population, intervention, comparison and outcome) framework was followed.

The electronic databases Cochrane Central, Web of Science, CINHAL, Embase and OVID Medline were searched from inception to 01/08/2023. Medical subject headings (MeSH) search terms were used and searches were conducted using free text, partial abbreviations, truncation, explosion and Boolean operators, such as "OR" and "AND".[19] The web-based software Covidence was used for the screening process and to facilitate the selection of studies. The first author (AG) conducted the database searches and screened retrieved papers by title and abstract with respect to the eligibility criteria. Duplicates were removed automatically by Covidence, or manually by the first author. The remaining full-text articles were screened independently by two reviewers (AG and RR), with any disagreements being resolved by discussion. A third reviewer (TH) moderated the decision where consensus was not reached. Reasons for exclusion of full-text articles were clearly recorded. Quality appraisal of the included studies was conducted independently by two reviewers (AG & TH), with the final quality appraisal being reached by consensus.

Table 1 PICO Framework

Population	Intervention	Comparison	Outcome
COPD patients on ICS therapy	Withdrawal of ICS therapy	Patients who withdraw ICS vs patients who continue ICS	• Rate of moderate or severe exacerbations • Change in lung function • Resumption of ICS therapy

Data Extraction

The data extracted from the articles included author/year, methods, treatment arms, participants (characteristics, disease severity, prior exacerbation history, trial run-in period, length of prior use of ICS therapy and exacerbation description), and outcomes (change in exacerbation frequency, change in lung function, resumption of ICS use).

Quality Assessment

The risk of bias of the randomised controlled trials was assessed using the Cochrane RoB2 tool,[20] whilst the quality assessment of the observational studies was assessed using the Newcastle-Ottawa Scale.[21] The grading of recommendations assessment, development, and evaluation approach (GRADE) was used to determine the quality of evidence for each outcome of the included RCTs.[22]

The risk of bias assessment was conducted independently by two reviewers, with any disagreements being resolved by discussion. The GRADE assessment was similarly conducted by two reviewers independently, with any disagreements being resolved by discussion. The quality of evidence from RCTs was deemed moderate for both outcome measures.

Meta Analysis

A post-hoc meta-analysis was undertaken to summarise the effect of ICS withdrawal on the exacerbation frequency and lung function of COPD patients stratified by blood eosinophil count thresholds of <300 cells/μL and ≥300 cells/μL. Cochran's Q test was used to assess between-study heterogeneity, where the true underlying effect varies between trials. We used the I^2 statistic to quantify this to give the proportion of overall variation accounted for by between-study heterogeneity. The assessment of clinical and methodological heterogeneity was conducted via discussion between authors. A random effects analysis was used where important heterogeneity was identified. Otherwise, a fixed-effects model was used which assumed each study measured the same underlying effect. The STATA version 17 was used for the statistical analysis.

Results

A total of 6729 papers were screened by title and abstract, after 1548 duplicates were removed. The reference list of included studies was also searched by title and abstract against the eligibility criteria to determine relevance to the review. One hundred and forty-nine papers were then screened by full text. Sixteen studies were included in the review (Figure 1); 10 RCTs and 6 observational studies. Search strategies are included in Supplementary Tables S2–S6.

Effect on Exacerbation Frequency

The earliest RCTs of ICS withdrawal (Table 2) reported either no difference in the frequency of moderate/severe exacerbations,[23] or an increased risk of exacerbations in the ICS withdrawal (placebo inhaler) vs ICS continuation arm.[24,25] More recent trials (Table 2) demonstrated that when bronchodilation (LABA or LABA+LAMA) was maintained after ICS withdrawal there was no difference in the exacerbation frequency between the trial arms.[11,26–30] Within the RCTs in which bronchodilation was maintained after ICS withdrawal, the annual mean exacerbation rate ranged from 0.15 to 1.6 exacerbations per patient-year in the ICS withdrawal arms and from 0.05 to 1.3 exacerbations per patient-year in the ICS continuation arms.[11,26,28–30] WISDOM, the largest ICS withdrawal trial, found no significant difference in the rate of moderate/severe exacerbations between the two arms.[28]

The evidence for stability in exacerbation frequency following ICS withdrawal was judged to be of moderate quality (Table S7). The trials were judged ineligible for meta-analysis due to their heterogeneity. Comparison showed clinical heterogeneity in the types of maintenance therapies provided to the patients in the ICS withdrawal arms of the RCTs, and variation in the definition of exacerbations between the studies (Table S7). In addition, there was marked variability in the prior exacerbation histories and degree of airflow limitation (FEV_1% predicted) among the patients of the RCTs. Prior exacerbation histories of patients across the trials ranged from zero[29] to at least two exacerbations[30] per patient-year (Table 3). The FEV_1% predicted values ranged from 34.3% (±10.8%)[28] to 73.53% (±14.12%)[11] and from 34.2% (±11.2%) to 72.79% (±14.12%) in the ICS withdrawal and continuation arms, respectively (Table 3). The duration of follow-up varied between trials. One was for 6 weeks,[23] two for 3 months,[27,31] four for 6 months[11,25,26,29] and three for 1 year.[24,28,30]

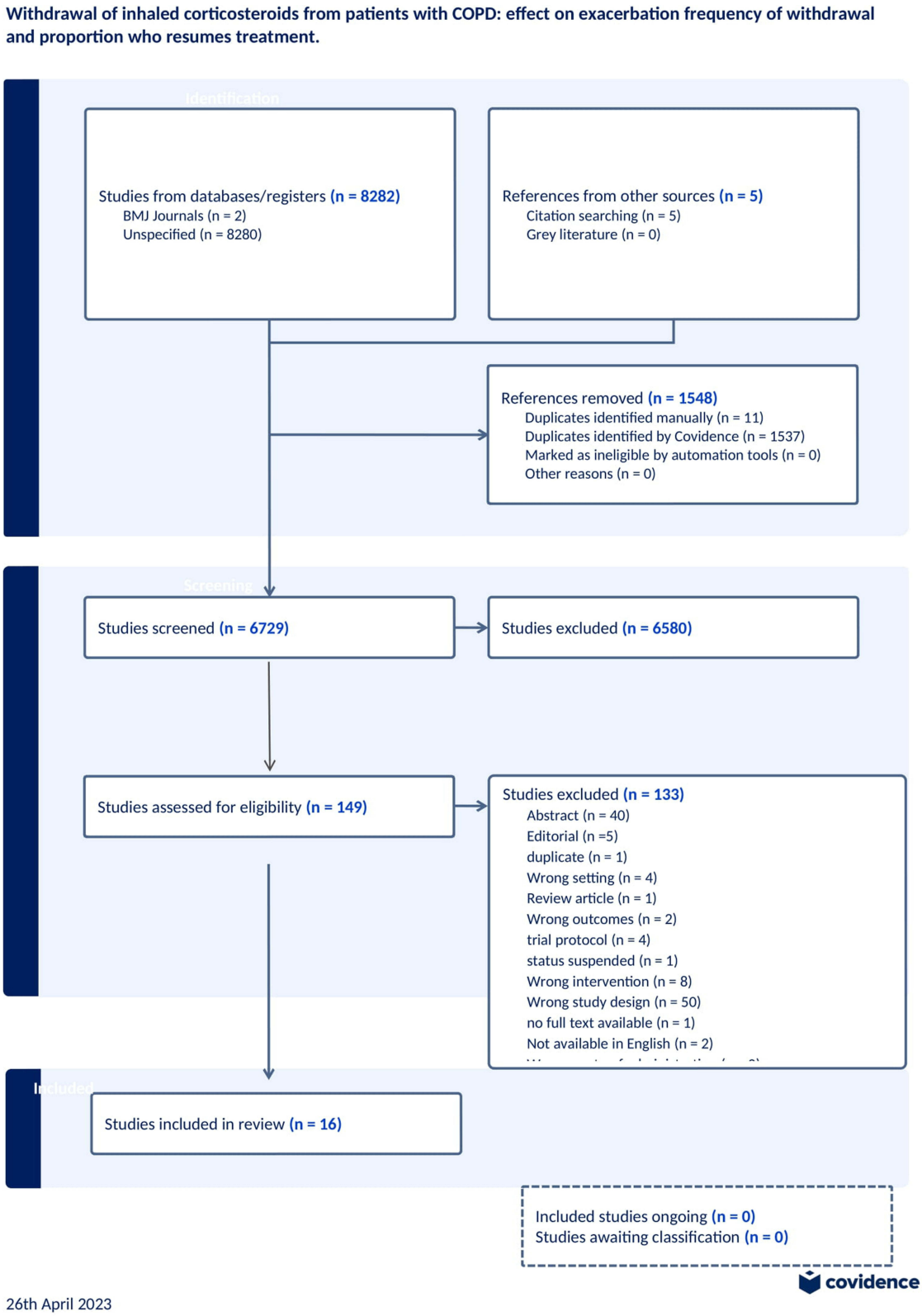

Figure 1 Withdrawal of inhaled corticosteroids from patients with COPD: effect on exacerbation frequency of withdrawal and proportion who resumes treatment.

Table 2 Outcomes of RCTs

Author/Year	Change in Moderate/Severe Exacerbation Frequency (Risk of Experiencing an Exacerbation)	Change in Lung Function (Post-Bronchodilatation FEV_1)	Resumption of ICS
O'Brien 2001[23] (ICS vs placebo)	No significant difference in rate of exacerbations between trial arms at 6 weeks. 17% in placebo vs 0 in steroid arm (p = 0.23).	Greater decrease in mean FEV_1 in placebo vs steroid arm at 6 weeks. Difference in mean decrease in FEV_1 of 0.1L (95% CI 0.002 to 0.195) between placebo vs steroid arm.	
Van Der Valk 2002[25] (ICS vs placebo)	Risk of first exacerbation in placebo vs steroid arm HR: 1.5 (95% CI 1.05 to 2.1) at 6 months. Proportion experiencing rapid recurrent exacerbations 26 (21.5%) patients in placebo vs 6 (4.9%) patients in steroid arm. RR: 4.4 (95% CI: 1.9 to 10.30)	No significant difference in decrease in mean FEV_1 between trial arms at 6 months. Difference in mean decrease in FEV_1 of 0.38L (−0.79 to 0.016) between placebo vs steroid arm.	
Choudhury 2007[24] (ICS vs placebo)	Intention to treat analysis: exacerbation risk in placebo vs steroid arm RR: 1.11 (95% CI 0.91 to 1.36) at 1 year. Per protocol analysis: exacerbation risk in placebo vs steroid arm HR: 1.48 (95% CI 1.17 to 1.86) at 1 year	No significant difference in decrease in mean FEV_1 between trial arms at 1 year. Difference in mean decrease in FEV_1 of 0.023L (p = 0.44) between placebo vs steroid arm.	46% patients in placebo arm resumed usual inhalers due to exacerbation or self-reported symptom worsening.
Wouters 2005[30] (ICS/LABA vs LABA)	No significant difference in rate of exacerbations between trial arms at 1 year. Annual exacerbation rate of 1.6 per patient year in withdrawal vs 1.3 per patient year in steroid arm. RR: 1.2 (95% CI 0.9 to 1.5).	Greater decrease in mean FEV_1 in ICS withdrawal vs continuation arm at 1 year. Adjusted difference in mean decrease in FEV_1 of 0.05L (95% CI: 0.01 to 0.1) between withdrawal vs steroid arm.	
Rossi 2014[29] (ICS/LABA vs LABA)	No significant difference in rate of exacerbations between the trial arms at 6 months. Annual exacerbation rate of 0.57 per patient year in withdrawal vs 0.67 per patient year in steroid arm. RR: 0.86 (95% CI 0.62 to 1.20)	No significant difference in decrease in mean FEV_1 between trial arms at 6 months. Difference in mean decrease in FEV_1 of 0.014L (95% CI −0.046 to 0.019) between withdrawal vs steroid arm.	
Vogelmeier 2017[31] (ICS/LABA vs LABA/LAMA)	Not reported.	Improvement in mean FEV_1 in ICS withdrawal vs continuation arm at 3 months. Difference in mean increase in FEV_1 of 0.071L (95% CI 0.036 to 0.107, p<0.0001) between in withdrawal vs steroid arm.	

(*Continued*)

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Table 2 (Continued).

Author/Year	Change in Moderate/Severe Exacerbation Frequency (Risk of Experiencing an Exacerbation)	Change in Lung Function (Post-Bronchodilatation FEV_1)	Resumption of ICS
Frith 2018[27] (ICS/LABA vs LABA/LAMA)	No significant difference in rate of exacerbations between the trial arms at 3 months. Reported exacerbations: 10.1% withdrawal vs 13.2% patients in steroid arm.	Improvement in mean FEV_1 in ICS withdrawal vs continuation arm at 3 months. Difference in mean increase in FEV_1 of 0.045L (95% CI 0.005 to 0.084) between withdrawal vs steroid arm.	
Magnussen 2014[28] (ICS/LABA/LAMA vs LABA/LAMA)	No significant difference in rate of exacerbations between the trial arms at 1 year. Adjusted exacerbation event rate 0.95 per patient year (95% CI 0.87 to 1.04) in withdrawal vs 0.91 per patient year (95% CI 0.83 to 0.99) in steroid arm (p>0.05).	Greater decrease in mean FEV_1 in ICS withdrawal vs continuation arm at 1 year. Difference in mean decrease in FEV_1 of 0.043L (p = 0.001) between withdrawal vs steroid arm.	
Chapman 2018[26] (ICS/LABA/LAMA vs LABA/LAMA)	No significant difference in rate of exacerbations between trial arms at 6 months. Exacerbation rate 0.52 per patent year in withdrawal vs 0.48 per patient year in steroid arm. HR: 1.08 (95% CI: 0.83 to 1.40).	No significant difference in decrease in mean FEV_1 between trial arms at 6 months. Difference in mean decrease in FEV_1 of 0.026L (95% CI −0.053 to 0.001) between withdrawal vs steroid arm.	
Harries 2022[11] (ICS/LABA/LAMA vs LABA/LAMA)	No significant difference in rate of exacerbations between trial arms. Exacerbation rate 0.15 (± 0.37) per patent year in withdrawal vs 0.05 (± 0.22) per patient year in steroid arm (p=0.30).	No significant difference in mean FEV_1% pred between trial arms at 6 months. FEV_1% pred 72.00 (±16.59) withdrawal arm vs 71.63 (±12.63) steroid arm.	21% patients in the ICS withdrawal arm resumed ICS therapy at 3-month review on medical advice due to their symptom deterioration and decline in FEV_1.

Abbreviations: bd, twice daily; qds, four times per day; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; FEV_1, Post-bronchodilatation Forced Expiratory Volume in 1 second.

Table 3 Characteristics of the RCTs

Author/ Year	Study Design	Treatment Arms	Characteristics	Disease Severity FEV_1 Mean (SD)	Exacerbation History Prior Year (mean (SD) Exacerbations Per Patient Year)	Run in Period	Length of Time of use of ICS prior to Study	Exacerbation Description (Moderate/Severe)
O'Brien 2001[23]	RCT, cross over. Withdrawal vs continuation. 6-week follow up	Beclomethasone dipropionate 336µg/day vs Placebo. (ICS vs placebo)	24 patients randomised. Age: 66.9 ± 1.9.	FEV_1 1.61 ± 0.1L (47% pred)	Details not provided	None	Details not provided	Details not provided
Van Der Valk 2002[25]	COPE RCT, parallel arms. Withdrawal vs continuation. Double blind 6-month follow up	Fluticasone propionate 500µg bd + ipratropium 50µg qds vs Placebo (ICS vs placebo)	244 patients randomised Age: 64.0 ± 7.2	Withdrawal arm: FEV_1: 1.69 ± 0.53L (56.1% ± 14.8% pred) Steroid arm: FEV_1: 1.78 ± 0.53L (57.5% ± 14.1% pred)	Withdrawal arm: 1.36 ± 1.66 Steroid arm: 1.31 ± 1.50	4 months use of fluticasone propionate 500µg bd + ipratropium 50µg qds	83% patients had used for at least 6 months	Worsening of respiratory symptoms requiring treatment with a short course of oral corticosteroids or antibiotics as judged by the study physician.
Choudhury 2007[24]	WISP RCT, parallel arms. Withdrawal vs continuation. Double blind 1-year follow-up	Fluticasone propionate 500µg bd vs Placebo (ICS vs placebo)	260 patients randomised Age: 67.6 vs 67.3, steroid vs withdrawal.	Withdrawal arm: 1.40 ± 0.56L (55.0% ± 17.1% pred) Steroid arm: 1.31 ± 0.55L (53.2% ± 18.2% pred)	Withdrawal arm: 1.48 ± 1.77 Steroid arm: 1.59 ± 1.71	2 weeks on patient usual medication	Minimum 6 months. Mean 8 years	Moderate: treated with a course of antibiotics or oral steroids. Severe: treated with a course of antibiotics or oral steroids and resulting in hospital admission.
Wouters 2005[30]	COSMIC RCT, parallel arms. Withdrawal vs continuation. Double blind 1-year follow-up.	Fluticasone propionate 500µg bd + Salmeterol 50µg bd vs Salmeterol 50µg bd (ICS/LABA vs LABA)	373 patients randomised. Age (mean) - 64 vs 63 (withdrawal vs continuation).	Withdrawal arm: 1.44 ± 0.42L (49% ± 11.6% pred) Steroid arm: 1.43 ± 0.49L (48.1% ± 11.6% pred)	Not specified but ≥2 documented exacerbations.	3-month use of fluticasone propionate 500µg bd + salmeterol 50µg bd	Details not provided	Moderate: course of oral corticosteroids indicated based on a clinician's judgment. Severe: admission to hospital.
Rossi 2014[29]	INSTEAD RCT. parallel arms. Withdrawal vs continuation. Double blind 6-month follow-up	Fluticasone propionate 500µg bd + Salmeterol 50µg bd vs Indacaterol 50µg/day (ICS/LABA vs LABA)	581 patients randomised.	FEV_1 (L) – 1.54 ± 0.40	Included patients with no exacerbations in the previous year.	2-week use of fluticasone propionate 500µg bd + salmeterol 50µg bd	≥3 months	Moderate: managed with course of antibiotics and/or oral corticosteroid. Severe: requiring hospitalisation.

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Table 3 (Continued).

Author/ Year	Study Design	Treatment Arms	Characteristics	Disease Severity FEV_1 Mean (SD)	Exacerbation History Prior Year (mean (SD) Exacerbations Per Patient Year)	Run in Period	Length of Time of use of ICS prior to Study	Exacerbation Description (Moderate/Severe)
Vogelmeier 2017[31]	CRYSTAL RCT. Open-label trial. 3-month follow-up.	Patients were randomised to either remain on baseline LABA/ICS (unspecified) vs Indacaterol/ Glycopyrronium 110/ 50µg/day (ICS/LABA vs LABA/ LAMA)	4389 patients randomised. 1080 patients compared (269 LABA/ICS, 811 LABA/LAMA) Age – patients aged ≥40 years included.	Withdrawal arm: 1.80 ± 0.50L (63.70% ± 8.07% pred) Steroid arm: 1.76 ± 0.50L (63.30% ± 8.30% pred)	≤1 Withdrawal arm: 72.4% had no exacerbations, 27.1% had ≥ 1. Steroid arm: 71.8% had no exacerbations, 26.8% had ≥ 1.	None	≥3 months	Moderate: requiring systemic corticosteroids and/or antibiotics Severe: requiring hospitalisation
Frith 2018[27]	FLASH RCT. parallel arms. Withdrawal vs continuation. Double blind 3-month follow-up	Fluticasone propionate 500µg bd + Salmeterol 50µg bd vs Indacaterol/ Glycopyrronium 110/ 50µg/day (ICS/LABA vs LABA/ LAMA)	502 patients randomised. Age – 65.0±9.14 vs 65.1±8.44, IND/GLY vs SFC.	Withdrawal arm: 51.3% ± 12.77% pred Steroid arm: 51.7% ± 12.73% pred	Withdrawal arm: 61.3% had no exacerbations, 38.7% had ≥ 1. Steroid arm: 59.2% had no exacerbations, 40.8% had ≥ 1.	None	≥3 months	Requiring treatment with antibiotics and/ or systemic corticosteroids and/or hospitalization.
Magnussen 2014[28]	WISDOM RCT. parallel arms. Withdrawal vs continuation. Double blind 1-year follow-up	Fluticasone propionate 500µg bd + Salmeterol 50µg bd + Tiotropium 18µg/day vs Salmeterol 50µg bd + Tiotropium 18µg/day (ICS/LABA/LAMA vs LABA/LAMA)	2485 patients randomised. Age – 63.8±8.5	Withdrawal arm: 0.98 ± 0.36L (34.3% ± 10.8% pred) Steroid arm: 0.97 ± 0.36L (34.2% ± 11.2% pred)	Not specified but ≥1 documented exacerbation	6 weeks on SFC 50/ 500µg bd + tiotropium 18µg/day	Details not provided. 69.4% of withdrawal arm and 70.5% of steroid arm using ICS prior to run in period	Moderate: increase in lower respiratory tract symptoms related to COPD or new onset of two or more such symptoms, with at least one symptom lasting ≥3 days, for which treating physician prescribed antibiotics, systemic glucocorticoids, or both. Severe: requiring hospitalization in an urgent care unit
Chapman 2018[26]	SUNSET RCT. Parallel arms. Withdrawal vs continuation. Double blind 6-month follow-up	Fluticasone propionate 500µg bd + Salmeterol 50µg bd + Tiotropium 18µg/day vs Indacaterol/ Glycopyrronium 110/ 50µg/day (ICS/LABA/LAMA vs LABA/LAMA)	1053 patients randomised. Age – 65.3±7.80.	Withdrawal arm: 1.60 ± 0.44L (56.2% ± 9.66% pred) Steroid arm: 1.60 ± 0.46L (57.0% ± 10.30% pred)	Withdrawal arm: 63.4% had no exacerbations, 36.6% had ≥ 1. Steroid arm: 68.4% had no exacerbations, 31.6% had ≥ 1.	4 weeks on SFC 50/ 500µg bd + tiotropium 18µg/day	≥6 months triple therapy	Moderate: treated with systemic corticosteroids and/or antibiotics. Severe: requiring hospitalisation in addition to treatment with systemic corticosteroids and/or antibiotics.
Harries 2022[11]	Feasibility RCT. Withdrawal vs continuation. Open label 6-month follow-up	Unspecified: ICS therapy (>400µg/ day beclomethasone dipropionate or equivalent) + LABA +LAMA vs LABA+LAMA (ICS/LABA/LAMA vs LABA/LAMA)	40 patients randomised. Age (years) – 70.10±9.22	Withdrawal arm: 1.77 ± 0.47L (73.53% ± 14.12% pred) Steroid arm: 1.87 ± 0.61L (72.79 ± 13.70% pred)	Withdrawal arm: 0.50 ± 0.51 Steroid arm: 0.45 ± 0.51	None	≥6 months triple therapy	Moderate: requiring treatment with antibiotics and/or oral corticosteroids in the community. Severe: requiring admission to hospital

Abbreviations: bd, twice daily; qds, four times per day; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; FEV_1, Post-bronchodilatation Forced Expiratory Volume in 1 second.

Risk of bias assessment found some concerns of bias arising from the randomisation process due to unclear allocation concealment in four trials;[11,23,25,30] some concerns of bias due to missing outcome data due to unclear risk of attrition bias in one trial;[23] and some concerns of bias in measurement of the outcome due to unclear risk of detection bias in five trials[11,23–25,30] (Figure 2).

Many of the observational studies described variability in the patient characteristics and treatment regimens (Table 4). All but one of the eligible observational studies reported no difference or a protective effect of ICS withdrawal with

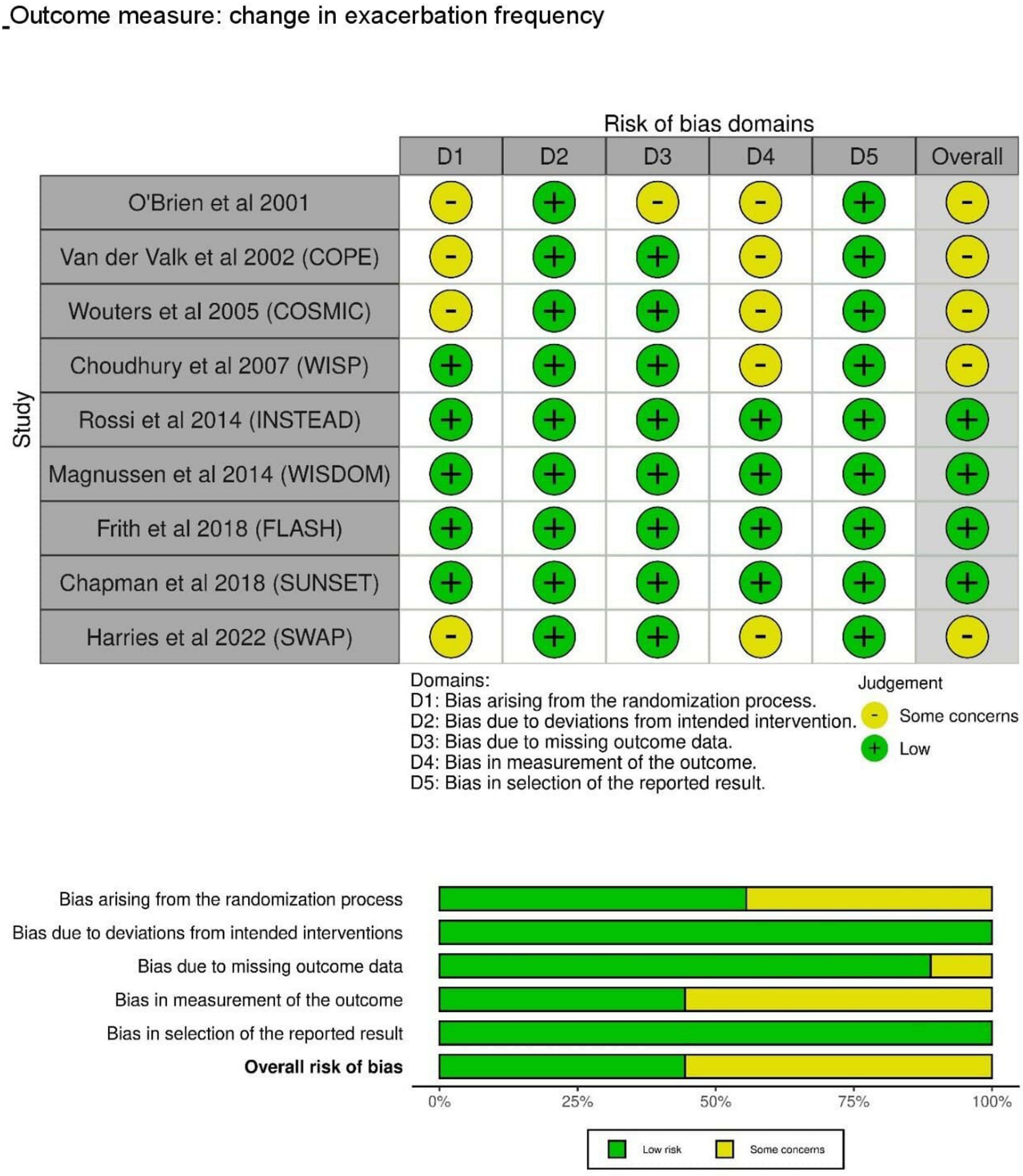

Figure 2 Risk of bias (ROB) summary of randomised controlled trials I for outcome measure change in exacerbation frequency.

Table 4 Characteristics of the Observational Studies

Author/ Year	Study Design	Treatment arms	Characteristics	Disease Severity FEV_1 /FEV_1% pred Mean (SD)	Exacerbation History Prior Year (Mean (SD) Exacerbations Per Patient Year)	Length of Time of Use of ICS Prior to Study	Exacerbation Description (Moderate/Severe)
Rossi 2014[32]	Non-randomised, prospective study of ICS withdrawal. 6-month follow-up	LABA/ICS vs LABA. At baseline: 56% using fluticasone/ salmeterol 500/50 mcg bd 18% using budesonide/ formoterol 400/12 mcg bd 12% using beclometasone/ formoterol 200/12mcg bd 14% using ICS and LABA from different inhalers	914 patients non-randomly allocated to either arm Age – 72.1±9.2 vs 73.0±8.9, withdrawal vs continue.	Withdrawal arm: FEV_1% pred 71.7% ± 10.4% Steroid arm: 70.8% ± 11.3%	Withdrawal arm: 36.7% had no exacerbations, 63.3% had ≥ 1. Steroid arm: 37.7% had no exacerbations, 62.3% had ≥ 1.	Regular treatment with ICS (frequency not specified)	A change in symptoms leading to a brief course of antibiotics or systemic corticosteroids or both, depending on what the treating physicians deemed fit, and which was reported on the patient's individual record
Vogelmeier 2017[33]	DACCORD. Retrospective observational study. 2-year follow-up	Baseline medication combinations included ICS monotherapy, LABA/ ICS, ICS/LAMA, LABA/ ICS/LAMA.	1365 patients entered the study, 236 patients in withdrawal arm vs 1022 patients in steroid arm. Age (mean) – 65.4 (10.9) vs 66.5 (9.7), ICS withdrawn vs steroid arm	Withdrawal arm: 1.80 ± 0.80L (67.40% ± 31.20% pred) Steroid arm: 1.60 ± 0.60L (59.80% ± 23.30% pred)	Prior 6 months: Withdrawal arm: 74.2% had no exacerbations, 25.4% had ≥ 1. Steroid arm: 29.0% had no exacerbations, 70.7% had ≥ 1.	Details not provided	Prescription of oral steroids and/or antibiotics or hospitalisation.
Magnussen 2021[34]	Retrospective observational study using the OPCRD database. 1 year follow-up.	LABA/ICS/LAMA vs LABA/LAMA.	5230 patients. Age – 70.7±10.2 vs 71.0±8.8, steroid vs withdrawal.	Withdrawal arm: FEV_1% pred 58.2% ± 20.9% Steroid arm: 53.9% ± 22.5%	Withdrawal arm: 1.1 ± 1.4 Steroid arm: 1.1 ± 1.4	≥2 fixed dose ICS/LABA and separate LAMA prescriptions, or ≥2 fixed dose ICS/LABA/ LAMA prescriptions, in the prior year	Unscheduled hospital admission or A&E attendance for COPD/respiratory condition or generic hospitalisation code on same day as a lower respiratory coded consultation, course of oral steroids and/or antibiotics prescribed with lower respiratory consultation.
Neches Garcia 2022[15]	Retrospective observational study using records from the BIG-PAC administrative database. 1 year follow-up.	LABA/ICS/LAMA vs LABA/LAMA.	6541 patients. Age (mean) – 70.5 ±10.8.	Withdrawal arm: FEV_1% pred 55.8% ± 14.1% Steroid arm: 52.2% ± 14.0%	Withdrawal arm: 0.4 ± 0.7 Steroid arm: 0.6 ± 0.9	Details not provided	Moderate: requiring treatment with antibiotics and/or oral corticosteroids. Severe: requiring hospitalisation.
Suissa 2022[35]	Retrospective observational study using CPRD data. 1 year follow-up.	LABA/ICS/LAMA vs LABA/LAMA.	85,334 patients. Age (mean) – 72.1 ±9.5 vs 71.9±9.3, withdrawl vs steroid.	Withdrawal arm: FEV_1% pred 53.7% ± 18.6% Steroid arm: 53.3% ± 18.5%	Withdrawal arm: 42.8% no exacerbations, 57.2% had ≥ 1. Steroid arm: 42.1% had no exacerbations, 57.9% had ≥ 1.	≥1 month	Moderate: prescriptions of prednisolone Severe: hospitalisations for COPD
Whittaker 2022[16]	Retrospective observational study using CPRD data.	LABA/ICS/LAMA vs LABA/LAMA.	60,645 General cohort of COPD patients Age (mean) – 69.5 ±9.5 vs 67.8±10.2 withdrawl vs steroid	Not specified Withdrawal arm: 6.2% had FEV_1% pred <30%. 27.2% had FEV_1% pred 30–49%. Steroid arm: 6.5% had FEV_1% pred <30%. 29.8% had FEV_1% pred 30–49%	Withdrawal arm: 39.7% had no exacerbations, 60.3% had ≥ 1. Steroid arm: 32.6% had no exacerbations, 67.4% had ≥ 1.	≥4 months triple therapy	Moderate: events recorded in primary care. Severe: events requiring hospitalisation

Abbreviations: bd, twice daily; qds, four times per day; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; FEV_1, Post-bronchodilatation Forced Expiratory Volume in 1 second.

respect to change in exacerbation frequency (Table 5).[32–34] Neches Garcia et al found an increase in the annual exacerbation rate within the ICS withdrawal in comparison to the ICS continuation group.[15] The results of the quality assessment of the observational studies are presented in Table S8. Five of the six studies were of high quality.[15,16,33–35] One study was of fair quality due to concerns of bias regarding its selection of controls, ascertainment of exposure and non-response rate.[32]

Effect on Lung Function

The RCTs which compared continuation of ICS therapy with use of placebo found either no difference[24,25] in change in lung function or an increased decline in lung function[23] among those participants who withdrew from ICS therapy (Table 2). The INSTEAD trial compared ICS continuation therapy with LABA monotherapy and reported no difference in change in lung function between the arms.[29] All but one of the trials which compared continuation of ICS therapy with use of dual-bronchodilation LABA/LAMA therapy reported either no difference in the change in lung function between the trial arms or an improvement favouring the ICS withdrawal arm.[11,26,27,31] Across the eligible trials, the difference in the change in mean FEV_1 between the trial arms ranged from 0.014L (95% CI −0.046 to 0.019)[29] to 0.38L (−0.79 to 0.016).[25]

The COSMIC[30] and the WISDOM[28] trials, which compared ICS continuation with LABA monotherapy and LABA/LAMA dual therapies, respectively, did report a significantly increased decline in lung function among the ICS withdrawal compared to the ICS continuation arms. The differences in change in lung function between the trial arms were 0.05L (95% CI: 0.01 to 0.1) in the COSMIC trial and 0.043L (p = 0.001) in the WISDOM trial. In both trials, the difference between the arms did not meet the threshold for the minimal clinically important difference (MCID) in change in lung function of 0.1L.[36]

The evidence for stability in lung function following ICS withdrawal was judged to be of moderate quality (Table S9). Risk of bias assessment found some concerns of bias arising from the randomisation process due to unclear allocation concealment in five trials;[11,23,25,30,31] some concerns of bias due to missing outcome data due to unclear risk of attrition bias in two trials;[23,31] and some concerns of bias in measurement of the outcome due to unclear risk of detection bias in six trials[11,23–25,30,31] (Figure 3).

The observational studies found no significant difference in the change in lung function between patients who withdrew from and those who continued using ICS therapy (Table 5).[16,34]

Resumption of ICS Treatment

Few of the studies included in this review reported on the proportion of patients who resumed ICS therapy following a trial of withdrawal. Only two of the RCTs[11,24] and three of the observational studies reported this finding.[33–35] The reported range of patients resuming ICS therapy following withdrawal was from 21% to 74%.[11,35]

Impact on Outcomes of the Stratification by Blood Eosinophil Count

Two RCTs, the SUNSET[26] and WISDOM[28] trials reported an association between blood eosinophil count and the impact of ICS withdrawal on exacerbation frequency and change in lung function among COPD patients. Both were post-hoc analyses and, in the case of the WISDOM trial, the findings were included in a later publication.[37] These post-hoc analyses were eligible for meta-analysis. Both trials included treatment arms of triple therapy vs dual-bronchodilation therapy. They both described the annualised exacerbation rate among participants. Among patients with COPD with a BEC ≥300 cells/μL, ICS withdrawal was associated with an increased exacerbation risk of 63% (RR, 1.63; 1.24–2.14) (Figure S1) and a decline in FEV_1 of 0.05L (RR, 0.05; 0.01–0.10) (Figure S2). ICS withdrawal was not associated with a change in exacerbation risk or a change in lung function in COPD patients with a BEC <300 cells/μL (Figures S3 and S4).

Table 5 Outcomes of Observational Studies

Author/Year	Change in moderate/severe exacerbation frequency (risk of experiencing an exacerbation)	Change in lung function (post-bronchodilatation FEV_1)	Resumption of ICS
Rossi 2014[32] LABA/ICS vs LABA.	No significant difference in rate of exacerbations between the trial arms. Exacerbations per patient per 6 months: 0.34 withdrawal arm vs 0.37 steroid arm. RR: 0.88 (95% CI: 0.68 to 1.14)	Change in mean FEV_1 between trial arms not reported. No significant difference in FEV_1% pred between trial arms at 6 months: 72.46% withdrawal vs 72.14% steroid arm (p=0.75)	
Vogelmeier 2017[33]	Fewer exacerbations in withdrawal vs steroid arm at 2 years. Annualised mean exacerbation rate: Year 1: 0.414 withdrawal vs 0.433 steroid arm (p>0.05) Year 2: 0.237 withdrawal vs 0.402 steroid arm (p<0.05)	Not reported.	45.3% patients in withdrawal arm.
Magnussen 2021[34] LABA/ICS/LAMA vs LABA/LAMA.	No significant difference in rate of exacerbations between the trial arms at 1 year. Annual exacerbation rate (mean (SD)): 1.01 (±1.46) per patient year in withdrawal vs 0.94 (±1.41) per patient year in steroid arm (p>0.05)	No significant difference in annualised change in FEV_1 (mean (SD)) between trial arms: -0.049L (±0.23) withdrawal vs −0.019L (±0.25) steroid arm (p>0.05)	61.9% in withdrawal arm.
Neches Garcia 2022[15] LABA/ICS/LAMA vs LABA/LAMA.	Increased exacerbations in withdrawal vs steroid arm. Annual exacerbation rate (mean (SD)): 0.50 (±0.80) per patient year in withdrawal vs 0.4 (±0.70) per patient year in steroid arm (p=0.018).	Not reported.	
Suissa 2022[35] LABA/ICS/LAMA vs LABA/LAMA.	Rate of total exacerbations between the trial arms not reported.	Not reported.	74% of withdrawal arm resumed ICS use
Whittaker 2022[16] LABA/ICS/LAMA vs LABA/LAMA.	Not reported.	No significant difference in decrease in mean FEV_1 between trial arms. Mean adjusted rate of FEV_1 decline withdrawal vs steroid arm: -0.008L (95% CI: −0.012 to 0.0041) vs −0.015L (95% CI: −0.019 to 0.012) (difference, p = 0.264)	

Abbreviations: bd, twice daily; qds, four times per day; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; FEV_1, Post-bronchodilatation Forced Expiratory Volume in 1 second.

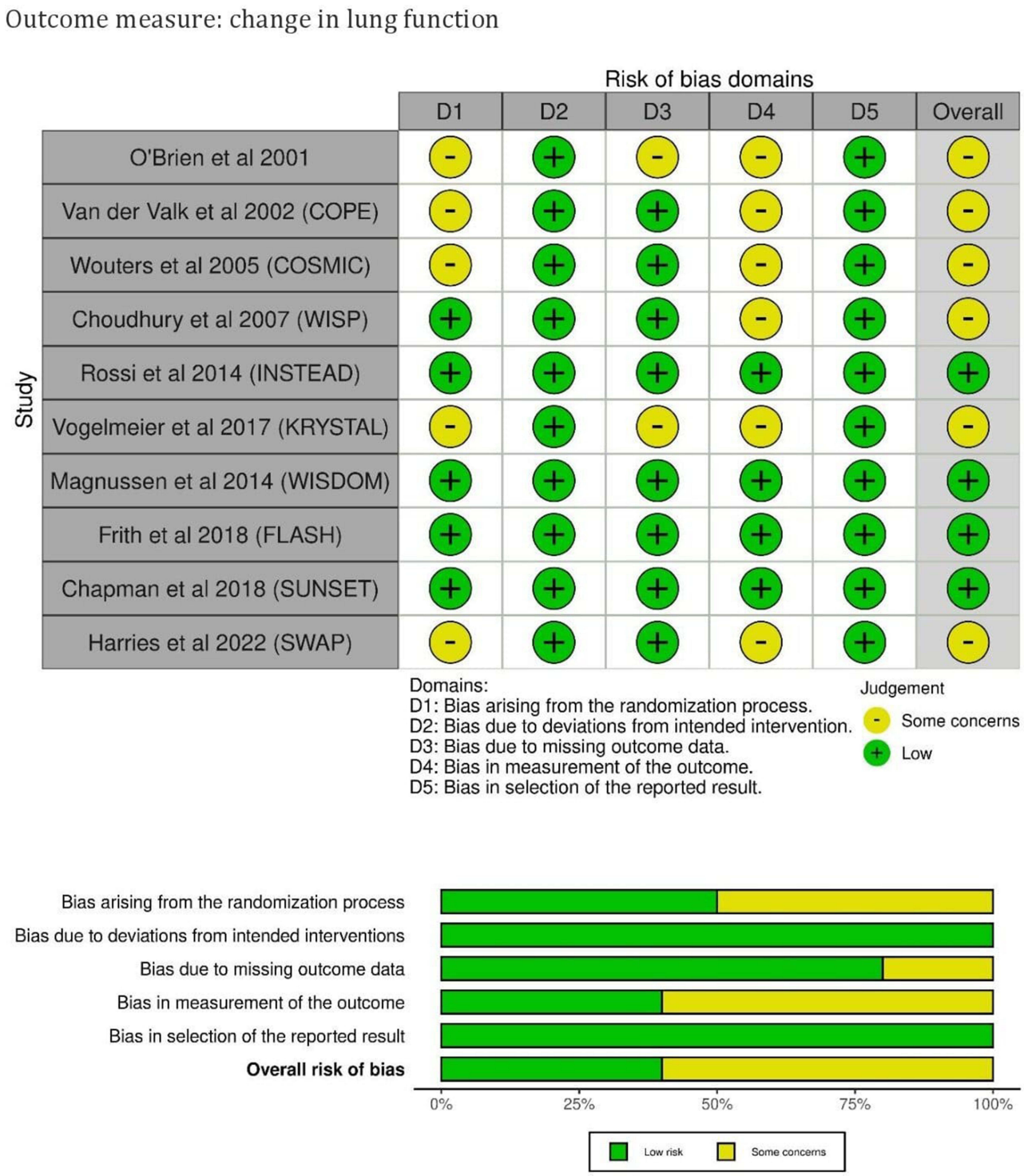

Figure 3 Risk of bias (ROB) summary of randomised controlled trials II for outcome measure change in lung function.

Discussion

This systematic review has identified a substantial number of studies which examined the impact of ICS withdrawal from patients with COPD. The earliest withdrawal studies, in which patients substituted ICS therapy for a placebo, did describe a worsening in the exacerbation frequency and a deterioration in lung function among patients withdrawn from ICS therapy compared with those who continued it. Newer studies in which participants maintained mono- or dual-bronchodilation

therapy after ICS withdrawal did not report a deterioration in health outcomes for COPD patients with respect to change in exacerbation frequency or lung function. This included the WISDOM trial which enrolled COPD patients with severe and very severe airflow limitation, historically those candidates for whom ICS therapy would have been recommended.[28] In two of the trials in which bronchodilation therapy was maintained following ICS withdrawal a statistically significant increased decline in lung function within the ICS withdrawal group was reported.[28,30] The decline in lung function may not be of clinical significance, as the change in FEV_1 was beneath the threshold for the minimal clinically important difference of 0.1L.[36] The effects on change in lung function and exacerbation frequency of withdrawal of ICS therapy, when bronchodilation was maintained, from COPD patients were minor. These findings were consistent across the majority of the RCTs and observational studies and the evidence was judged to be of high to moderate quality.

Few studies have reported the prevalence of resumption of ICS therapy after a trial of withdrawal, an important consideration for all clinicians who attempt ICS withdrawal in clinical practice.

In the RCTs and observational studies which did report this outcome, the analyses of rates were unclear and inconsistent between studies. The studies varied with regard to the types of replacement inhalers provided to those who withdrew from ICS therapy, the degree of airflow limitation among participants, differences in their prior exacerbation histories and the length of follow-up per study. An accurate estimate would best be derived from a prospective trial. The paucity of data reported on the resumption of ICS therapy and the wide range in prevalence among those studies that reported this finding, makes it difficult to provide a firm estimate by which to guide clinical practice.

The findings from the majority of the studies included in this review were not appropriate for meta-analysis due to major differences in study populations and methodology. Many withdrawal studies had different treatment arms, preventing statistical comparison. There was heterogeneity between trials in terms of sample size, differing inclusion criteria, definition of exacerbation and type of replacement therapies following ICS withdrawal. Participants in many studies had substantial differences in age, lung function, and exacerbation histories. Many studies included different types and dosages of steroid therapies, with variation in the treatment strategies, run-in periods, and types of ICS therapy used by the participants prior to study enrolment.

The meta-analysis, obtained from post-hoc analyses of the WISDOM and SUNSET trials,[26,37] provides evidence of lung function decline and an increased risk of exacerbations among those patients with COPD with BEC ≥300 cells/μL who withdrew from ICS therapy. The findings suggest that in COPD patients without a history of frequent prior exacerbations (<2 exacerbations per year) and with a BEC <300 cells/μL, ICS withdrawal is safe and feasible, provided patients also receive maintenance therapy with either mono- or dual-bronchodilation. This supports the GOLD recommendations for ICS prescription within this group.[6] The follow-up periods after ICS withdrawal included in the post-hoc analyses varied between the two included trials.[26,37] In the WISDOM trial,[37] the 9-month period after complete withdrawal of ICS was included, while a 6-month period was included in the SUNSET trial.[26] The demographic characteristics of the participants of the two trials differed. The participants included in the analysis of the WISDOM trial had a mean FEV_1% predicted of 34.2% ± 11.0 and all had experienced at least one moderate or severe exacerbation in the year prior to the trial. The participants included in the analysis of the SUNSET trial had a mean FEV_1% predicted of 56.6% ± 9.97 and 34% of the participants had experienced one moderate or severe exacerbation in the past year.

Our findings are supported by those of previous systematic reviews. Nadeem et al looked at the effects of withdrawal of ICS therapy from patients with COPD in RCTs that compared ICS withdrawal with continuation. The review included four RCTs (WISP, COPE, COSMIC, O'Brien et al, 2001).[13] They found no statistically significant difference in exacerbation frequency. Change in lung function was only found to be statistically significant in the COSMIC trial (but did not reach the threshold of the MCID).[13] In 2020, a review by Chalmers et al reported similar findings from a broader range of trials.[9] Again, no statistically significant difference was found in exacerbation frequency between ICS continuation and ICS withdrawal and, whilst the change in lung function was statistically significant, this did not meet the threshold for the MCID.[36] A recent scoping review of ICS withdrawal suggested that adverse effects of withdrawal were more common following abrupt withdrawal in comparison to gradual withdrawal.[38]

The current systematic review is the first to compare randomised controlled trials and observational studies of ICS withdrawal in COPD. The meta-analysis of the impact of withdrawal of ICS therapy with respect to exacerbation frequency and change in lung function among patients with COPD stratified by blood eosinophil count is novel.

Heterogeneity between the ICS withdrawal studies in participant characteristics, factors that may influence the impact of ICS withdrawal, prevented inclusion of most studies in the meta-analysis. Another limitation of the review was that follow-up times were not compared between the studies to understand whether time since ICS withdrawal modified the relationship between withdrawal and the outcome measures. Confounding is a possible limitation in the interpretation of the results of the observational studies. However, in most of the observational studies the ICS withdrawal group had either similar[32,35] or poorer baseline morbidity,[33,34] with respect to symptom severity[33] or prior exacerbation history,[34] but showed no adverse outcome in comparison to the continuation group. One observational study did report a worsening in exacerbation rate among those who withdrew from ICS therapy.[15] These participants had less severe airflow limitation at baseline and fewer prior exacerbations compared to those in the continuation group.

Conclusions

Withdrawal of ICS from COPD patients is safe and feasible without a detrimental impact on exacerbation frequency and decline in lung function among the majority of COPD patients. Withdrawal of ICS therapy should be accompanied by maintenance of bronchodilation therapy for optimal outcomes. Patients with frequent exacerbations (≥2 per year) and a BEC ≥300 cells/μL may benefit from continued ICS use. These findings provide clinicians with the confidence to withdraw ICS therapy from COPD patients for whom it has been inappropriately prescribed. There is a need for prospective trials, both RCTs and observational studies using routinely collected data, which identify the characteristics of those in whom ICS withdrawal should not be attempted. Details such as the patient's exacerbation history, lung function, exercise capacity, physical activity and health status could all possibly be used to determine whether withdrawing ICS from these patients with COPD is feasible. Further research may outline more clearly the criteria that a patient needs to fulfil to increase clinicians' confidence that withdrawal of ICS will be safe.

Abbreviations

COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; FEV1, forced expiratory volume in 1 second; OCSs, observational cohort studies; RCTs, randomised controlled trials; LAMA, long-acting muscarinic antagonists; LABA, long-acting beta agonists; MCID, minimal clinically important difference.

Data Sharing Statement

All data generated or analysed during this study are included in this published article [and its Supplementary Information Files].

Disclosure

THH and PW were co-authors of the study Harries TH, Gilworth G, Corrigan CJ, et al. Withdrawal of inhaled corticosteroids from patients with COPD with mild or moderate airflow limitation in primary care: a feasibility randomised trial. *BMJ Open Respir Res*. 2022;9(1):e001311. doi:10.1136/bmjresp-2022-001311. They have recused themselves from any involvement in the assessment of the risk of bias in this study. The authors report no other conflicts of interest in this work.

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