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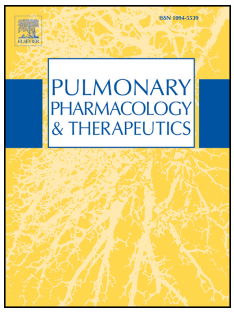

Withdrawal of inhaled corticosteroids in COPD: A meta-analysis

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PII: S1094-5539(17)30125-6

DOI: 10.1016/j.pupt.2017.06.002

Reference: YPUPT 1636

To appear in: *Pulmonary Pharmacology & Therapeutics*

Received Date: 4 May 2017

Accepted Date: 7 June 2017

Please cite this article as: Calzetta L, Matera MG, Braido F, Contoli M, Corsico A, Di Marco F, Santus P, Scichilone N, Cazzola M, Rogliani P, Withdrawal of inhaled corticosteroids in COPD: A meta-analysis, *Pulmonary Pharmacology & Therapeutics* (2017), doi: 10.1016/j.pupt.2017.06.002.

Withdrawal of inhaled corticosteroids in COPD: a meta-analysis

Short title

ICS discontinuation and COPD

Registration

PROSPERO 2017:CRD42017057519

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Conflict of interest

LC has participated as advisor in scientific meetings under the sponsorship of Boehringer Ingelheim, received non-financial support by AstraZeneca, received a research grant partially funded by Boehringer Ingelheim, Novartis and Almirall, and is or has been a consultant to Zambon and Verona Pharma.

MGM has participated as a lecturer, speaker, and advisor in scientific meetings and courses under the sponsorship of Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline and Novartis, and has been a consultant to Chiesi Farmaceutici.

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The Department of Systems Medicine of the University of Rome "Tor Vergata" was funded by Almirall, Boehringer Ingelheim, to Chiesi Farmaceutici, Novartis, and Zambon to conduct research in the respiratory field.

Key points

Question

Does withdrawal of ICS impair the risk of exacerbation, lung function and quality of life of COPD patients?

Findings

ICS withdrawal did not significantly increase the overall rate of COPD exacerbation, although a clinically important increased risk of severe exacerbation was detected. ICS withdrawal significantly impaired both lung function and quality of life, although in a non-clinically important manner.

Meaning

High-quality evidences concerning the impact of ICS withdrawal in COPD.

Abstract

Background

Conflicting findings exist on the benefit of withdrawal of inhaled corticosteroid (ICS) in chronic obstructive pulmonary disease (COPD). We performed a quantitative synthesis in order to assess real impact of ICS discontinuation in COPD patients.

Methods

We carried out a meta-analysis via random-effects model on the available clinical evidence to evaluate the effect of ICS discontinuation in COPD. Randomized clinical trials and observational real-life studies investigating the effects of ICS withdrawal on the risk of COPD exacerbation, lung function (forced expiratory volume in one second [FEV_1]) and quality of life (St. George's Respiratory Questionnaire [SGRQ]) were identified by searching from published studies and repository databases.

Results

ICS withdrawal did not significantly ($P>0.05$) increase the overall rate of COPD exacerbation, although a clinically important increased risk of severe exacerbation was detected (Relative Risk >1.2). ICS withdrawal significantly ($P<0.001$) impaired both lung function (-30 ml FEV_1) and quality of life (+1.24 SGRQ units), although in a non-clinically important manner. The time to the first exacerbation was significantly ($P<0.05$) shorter in the patients who discontinued ICS.

Conclusions

The discrepancy between statistical analysis and clinical interpretation of this meta-analytic evaluation demonstrates the strong clinical need in understanding what is the real impact of ICS withdrawal in COPD. ICS discontinuation is a complex procedure that requires a well planned and tailored strategy. Further well designed studies on withdrawal of ICS should be performed by clustering COPD patients with regard to the phenotype characteristics, rate of exacerbations/year, decline of lung function, and quality of life.

Keywords

Inhaled corticosteroids; withdrawal; chronic obstructive pulmonary disease

Introduction

The impact of inhaled corticosteroid (ICS) discontinuation in chronic obstructive pulmonary disease (COPD) has been investigated in several randomized clinical trials (RCTs) and real life studies since 2001. Nevertheless, to date conflicting findings and opinions remain on the real benefit of withdrawal of ICS. In fact, while several RCTs reported that COPD patients may be at increased risk of exacerbation, deterioration of quality of life and lung function after ICS discontinuation [1-4], the data from two real life studies indicated that withdrawal of ICS can be safe and with no increased risk of exacerbations [5, 6]. Conversely, the results of a large RCT indicated that the risk exacerbations was similar among COPD patients who discontinued ICS and those who continued glucocorticoid therapy [7], whereas an observational prospective study concluded that ICS discontinuation can worsen lung function decline, airway hyperresponsiveness and quality of life [8]. Reassurance in ICS withdrawal was further provided by another RCT that enrolled low exacerbation risk patients [9].

ICS are widely prescribed across all the levels of COPD severity and exacerbation risk, with a rate of over-prescription that is two fold higher than that expected by following guidelines or recommendations such as the Global Initiative for Chronic Obstructive Lung Diseases (GOLD), although since 2007 it was suggested to limit the use of ICS in patients with reduced lung function and/or high exacerbation rate [10]. Nevertheless, the last version of the GOLD recommendation (2017) has highlighted that the studies on withdrawal of ICS produced equivocal results, and suggested that differences among the studies may be related with differences in methodology [11].

In this confusing scenario, we have carried out a quantitative synthesis via meta-analysis of the currently available data in order to provide consistent and homogeneous findings that may help to better clarify the real impact of ICS discontinuation in COPD patients, especially with regards to the risk of exacerbation, lung function and quality of life.

Materials and methods

Detailed meta-analytic methods are reported in the online Supplemental Materials.

Search strategy and study eligibility

This meta-analysis has been registered in PROSPERO (CRD42017057519), and performed in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Figure 1, Table S1) [12, 13].

We undertook a comprehensive literature search for studies on ICS withdrawal in COPD patients. Published and unpublished RCTs and non-RCTs (observational real-life studies) were searched in PubMed, Scopus, Embase and Google Scholar and the repository databases clinicaltrials.gov and EU Clinical Trials up to February 1, 2017 [14].

End points

The primary endpoints have been chosen in agreement with the availability of variables characterized by a documented minimal clinical important difference (MCID). The MCID have been considered as the noninferiority margin discerning the impact between ICS withdrawal and ICS continuation. The primary endpoints were the risk of COPD exacerbation (MCID: 20% difference in frequency or 1.20 Hazard Ratio [HR], that describes the Relative Risk [RR] [7, 15, 16]), change in FEV_1 (MCID: 100 ml difference [15, 17]) and SGRQ (MCID: 4 units difference [15, 17]). The secondary endpoints, for which no MCID are currently available, were the risk of at least one exacerbation and the time to the first exacerbation.

Quality score, risk of bias and evidence profile

The Jadad score was used to assess the quality of the RCTs and the risk of publication bias assessed via funnel plot and Egger's test [18]. The quality of the evidence was assessed via the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [19].

Data analysis

This pair-wise meta-analysis has been performed via random-effects model [20]. The data on exacerbation have been normalized as a function of person-season. Results have been reported as RR, Mean Difference (MD) Standardized MD (SMD), and 95% confidence interval (95%CI). A subset analysis was carried out by excluding the non-RCTs and including only high quality studies. The optimal information size (OIS) was calculated as previously described [21]. The statistical significance was assessed for $P<0.05$.

Results

Studies characteristics

Results obtained from 6,066 COPD patients were selected from 10 published studies Table 1 [1-9, 22]. Table 2 shows the definition of exacerbation as reported by analyzed. Further results are reported in the online Supplemental Materials.

Meta-analysis

Primary endpoints

Overall, the withdrawal of ICS did not significantly (P>0.05) affect the risk of COPD exacerbations. However, the subset analysis including only RTCs shown that, although in a non-significant manner (P>0.05), there was a potentially clinically relevant increased risk of moderate-to-severe COPD exacerbations in patients that discontinued ICS compared to those who continued ICS. In fact, 2.38% and 33.62% of the RR 95%CI of moderate and severe COPD exacerbation exceeded the noninferiority margin, respectively (Figure 2A). Withdrawal of ICS significantly affected both FEV_1 (P<0.001) and SGRQ (P<0.05), as confirmed by the synthesis performed exclusively on RCTs, and the 95%CI limits did not overlap the noninferiority margin (Figure 2B and C). Further details on the forest plots of primary endpoints are reported in the online Supplemental Materials (Figures S1 – S3).

Secondary endpoints

The risk of experiencing at least one exacerbation of COPD was irrespective of the use of ICS (P>0.05), although a higher risk was detected in the subset analysis performed on RCTs. The time to the first exacerbation was significantly (P<0.05) shorter if COPD patients discontinued ICS, compared to those who continued ICS (Figure 3A and B). Further details on the forest plots of secondary endpoints are reported in the online Supplemental Materials (Figures S4 and S5).

Bias and quality of evidence

No significant heterogeneity was detected for the risk of COPD exacerbations and change in SGRQ (both P<0.05), whereas significant (P<0.01) high level of heterogeneity was found for FEV_1 (I^2 79%, P<0.001). Nevertheless, neither funnel plot nor Egger's test detected any publication bias with regard to the primary endpoints (Figure 4A – F). The cumulative number of enrolled patients reached the OIS for either the risk of COPD exacerbations and change in FEV_1, but not for SGRQ (OIS: 4,200; delta -2,664).

The GRADE approach indicated high quality of evidence for all the investigated primary endpoints (Table 3). This outcome indicate that the results of this synthesis are robust and reliable.

Discussion

The results of this meta-analysis demonstrates that ICS withdrawal did not significantly increase neither the overall risk of COPD exacerbation, nor the risk of moderate-to-severe exacerbations, although the time to the first exacerbation was significantly shorter in patients who discontinued ICS compared to those who continued the treatment. However, a signal of higher risk of experiencing at least one exacerbation was detected in patients enrolled in RCTs who discontinued ICS. Furthermore, withdrawal of ICS significantly impaired both the FEV_1 and SGRQ. These findings may suggest that the discontinuation of ICS could be a safe procedure that does not influence the risk of exacerbation, although some concern may remain with regard to the impact on lung function and quality of life. ICS withdrawal in our results also demonstrates consistent effect estimates that may be obtained by both RCTs and real life studies.

Certainly, the effects estimates resulting from a meta-analytic synthesis have to be primarily evaluated by a strict statistical point of view, although this approach may lead to inaccurate clinical conclusions. Describing the findings by evaluating only the statistical significance (P value <0.05) provides information on the probability of rejecting the null hypothesis. Unfortunately, the P values are often misused, misinterpreted and, thus, should not represent the basis for drawing clinical decisions [23].

On the other hand, evaluating the 95%CI values with regard to predetermined MCIDs may represent a suitable approach to assess if there is a reasonable possibility that the investigated outcomes would reach a clinical relevant magnitude. In fact, since it is expected that 95%CI includes the true population mean in 95% of the cases, if the upper or lower confidence intervals overlap a noninferiority criterion, there is 95% chance that also the real population mean will overlap the noninferiority level, independently by the P value [24]. Thus, the correct interpretation of the 95%CI values reported in this meta-analysis permits to clearly identify the real clinical impact of ICS discontinuation. This implies that the effect estimates resulting from this quantitative synthesis have to be related with the MCIDs available for the primary endpoints, namely the risk of COPD exacerbation and changes in FEV_1 and SGRQ.

Since the results of this synthesis are unbiased, robust and reliable by a meta-analytic point of view, we can interpret the findings obtained on the primary endpoint of this study also by a clinical perspective. In fact, to date the MCID values are available for either the risk of exacerbation, change in FEV_1 and SGRQ. In order to correctly analyze the minimum beneficial effect to be considered be clinically relevant, we have predetermined the primary endpoints and key information about the design of this quantitative synthesis in the international repository database PROSPERO. Thus, considering the clinical impact of ICS discontinuation, our study clearly demonstrates that the upper 95%CI value of the risk of moderate exacerbation overlapped of a little extent the prespecified noninferiority criterion of 1.20, and that more than ≈33% possibility exists that withdrawal of ICS may increase the risk of severe exacerbation. Conversely, although pulmonary function and quality of life were

affected in the ICS-withdrawal group compared to the ICS-continuation group, the magnitudes of changes in both FEV_1 and SGRQ values were far from their predefined MCIDs, respectively 100 ml and 4 units differences.

In our opinion, the discrepancies between the statistical and clinical interpretation of the impact of ICS withdrawal in COPD patients highlights the relevance of correctly interpreting the findings obtained via a meta-analytic approach. Nadeem and colleagues have previously attempted to determine the effect of withdrawal of ICS in individuals with COPD through a meta-analysis [25], and concluded that there was no significant evidence that withdrawing ICS in routine practice results in important deterioration in patient outcomes. Although that meta-analysis [25] was characterized by several methodological weaknesses, such as the lack of bias and quality assessment, and the paucity of data available in 2011, the Authors yet evidenced that the definition of exacerbations was not consistent between the analyzed studies, and the impact of withdrawal was smaller in the trials which were conducted under conditions that reflected routine practice [25]. Unfortunately, although we can now provide a robust synthesis of the impact of ICS discontinuation obtained from the analysis of more than 5,400 COPD patients, nowadays the issue of the lack of a clear definition of COPD exacerbation still exists. In fact, we have found no consistency in the definition of COPD exacerbation among the analyzed studies, and two studies did not even report it [2, 8].

Despite this objective limitation, that represents an extrinsic factor from the meta-analytic approach, the high quality findings of this quantitative synthesis allow us to ultimately assert that, to date, a reasonable doubt exists on the real advantage and safety of withdrawing ICS in COPD patients. Our findings suggest that the current question should not be understanding if ICS can be suspended or not in COPD, but identifying which patients with COPD do not require the therapy with an ICS-regimen, or rather which is the subset of patients with COPD that can benefit from ICS therapy. In fact, we cannot omit that this meta-analysis pointed out that there is a small, although possible, chance that a portion of the studied population may have a reduced risk of COPD exacerbation after withdrawal of ICS.

A further strategy option for approaching the withdrawal of ICS may be to switch toward double bronchodilation. In fact, the FLAME study has recently demonstrated that combining a long-acting β_2-AR agonists (LABA) with a long-acting antimuscarinic agent (LAMA) may be more effective than ICS/LABA combination in preventing exacerbations of chronic obstructive pulmonary disease in COPD patients. [66]. Nowadays there is a considerable amount of evidence that small airway inflammation contributes importantly to the clinical expression of COPD [26]. Although ICSs are effective in ameliorating inflammation at the level of both large and small airways, with consequent improvement of airflow, recent studies proved that also bronchodilators may have a remarkable bronchorelaxant effect on small airways, especially when administered in combination [27, 28]. Furthermore, it has been well documented that most patients with COPD respond poorly to ICSs, as the inflammatory process in COPD is resistant to the anti-inflammatory effect of corticosteroids [29]. Combining two bronchodilators

with different mechanisms of action reduces the release of non-neuronal acetylcholine from airway epithelium [30]. Considering the ubiquitous pro-inflammatory activity of non-neuronal acetylcholine, and its specific role in remodeling and modulating the inflammatory processes in diseases like those that include the bronchial obstruction component [31, 32], counteracting the release of non-neurogeinc acetylcholine and antagonizing their receptors through antimuscarinic agents combined with β_2-AR agonists may lead to anti-inflammatory effects at the level of small airways.

Indeed we provide the findings that ICS discontinuation is a complex procedure that requires a well planned strategy. De-escalating from ICS by adding no further medications may be a suitable approach in not frequent exacerbator COPD patients that are characterized by an acceptable quality of life and slow decline in lung function. On the other hand, in those patients who have a high rate of exacerbation per year, poor quality of life and rapid airflow decline, we should take into account the possibility of a reduced responsiveness to the anti-inflammatory effects of corticosteroids, due to the reduced activity and expression of histone deacetylase caused by the oxidative stress [33]. Certainly, in the case of corticosteroid resistance there is no pharmacological rationale for administering an ICS, and the inhalant therapy should be switched toward LABA/LAMA combination. This therapeutic approach is in agreement with the pharmacological treatment algorithm proposed by the last GOLD recommendations (2017, Figure 4.1), that has indicated the LABA/LAMA combination as the preferred treatment for the Group B, C and D patients. Whereas, the administration of an ICS has been recommended only in the Group D patients yet treated with LABA/LAMA combination that have further exacerbations(s) [11]. Nevertheless, it has been recently highlighted [34] that two large RCTs, the TRILOGY and TRINITY studies [35, 36], have provided the evidence for the efficacy of LABA/LAMA/ICS combination therapy in Group B patients, that are highly symptomatic but at low risk of exacerbations, for whom the current recommendations do not suggest to includes an ICS [11].

Conclusions

Although the current large body of evidence available from both RTCs and real life studies, even a large and rigorous meta-analysis did not allow to bridge the scientific gap concerning the discontinuation of ICS in COPD. This study highlights the strong clinical need of well designed studies aimed to investigate the impact of ICS withdrawal by clustering CODP patients with regard to at least the phenotype characteristics (i.e. frequent exacerbator, emphysema-hyperinflation and COPD with an asthma component), the rate of exacerbations/year (i.e. <1; ≥1 and ≤2; >2), the decline of lung function (rapid decliners vs. slower decliners) and the quality of life [37]. This approach would lead to significant benefit for patients, by providing an attempt of tailored medicine aimed to optimize the pharmacological therapy of COPD.

Acknowledgments

Guarantor

LC and PR have the responsibility for the content of the manuscript, including the data and analysis.

Author contributions

LC and PR contributed to study conception and design; contributed to acquisition, analysis, and interpretation of data; drafted the submitted article and revised it critically for important intellectual content and provided final approval of the version to be published.

MGM and MCa contributed to study design; contributed to interpretation of data; drafted the submitted article and revised it critically for important intellectual content and provided final approval of the version to be published.

FB, MCo, AC, FDM, PS and NS revised the submitted article critically for important intellectual content and provided final approval of the version to be published.

Financial/non-financial disclosures

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Role of the sponsors

Sources

This study was supported by institutional funds (University of Rome “Tor Vergata”, Rome, Italy).

Sponsor

Not applicable

Role of sponsor/funder

No sponsor/funder had a role in the design of the study, the collection and analysis of the data, or in the preparation of the manuscript.

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Table 1. Patient demographics, baseline and study characteristics.

Study, year and reference	Trial Number Identifier	Study characteristics	Study duration (weeks)	Number of analyzed patients	Treatment during the run-in period	Trial period medication		Patients characteristics	Age (years)	Male (%)	Current smokers (%)	Smoking history (pack-years)	Post-bronchodilator FEV_1 (% predicted)	Duration of inhaled steroid use prior to entry into trial	Baseline number of exacerbations in year preceding trial	Jadad score
					Treatment	Steroid group	Withdrawn group									
Vogelmeier, 2016 [6]	EUPAS4207	Prospective, noninterventional study	104	1258	ICS, ICS/LABA, ICS/LAMA, ICS/LABA/LAMA, ICS plus PDE4 inhibitor or theophylline.	ICS, ICS/LABA, ICS/LAMA, ICS/LABA/LAMA, ICS plus PDE4 inhibitor or theophylline	LABA, LAMA, LABA/LAMA, PDE4 inhibitor or theophylline	COPD, post bronchodilator FEV_1/FVC ratio <70%, change in FEV_1post-bronchodilator pre-bronchodilator <15% or 200 ml.	65.5	59.1	30.7	NA	63.6	NA	NA	NA
Kunz, 2015 [8]	NCT00158847	Randomized, double-blind, placebo-controlled.	260	52	Fluticasone (500 mg bid), fluticasone/salmeterol (500/50 mg bid).	COPD treated in agreement with guidelines: patients continued using ICSs 50% to 100% of the time. Daily dose in beclomethason dipropionate equivalents: 960 µg.	COPD treated in agreement with guidelines: patients stopped using ICSs.	Moderate to severe COPD.	64.5	89.4	50.0	46.0	63.5	6 months to 30 months	NA	NA
Magnussen, 2014 (Rodriguez-Roisin, 2016) [7, 22]	NCT00975195	Randomized, double-blind, parallel, active-control study.	52	2485 (1573)	Tiotropium (18µg qd), salmeterol xinafoate (50 µg bid), fluticasone proprionate (500 µg bid).	Tiotropium (18 µg qd), salmeterol xinafoate (50 µg bid), fluticasone proprionate (500 µg bid).	Tiotropium (18µg qd), salmeterol xinafoate (50 µg bid), stepwise reduction in the fluticasone propriona te dose every 6 week, from total daily dose of 1000 µg to 500 µg, then 200 µg	Severe or very severe COPD, FEV_1<50 % of the predicted volume and FVC <70% post-bronchodilation.	63.8	82.5	33.4	≥10	34.2	6 weeks	≥1	4

							and finally 0 µg.								
Rossi, 2014 [9]	NCT01555138	Multinational, multicentre, randomized, double-blind, double-dummy, parallel group	26	581	Salmeterol/fluticasone (50/500 µg bid)	Salmeterol/fluticasone (50/500 µg bid)	Indacaterol (150 µg qd)	Moderate COPD (stage II as defined in the GOLD 2010 criteria)	65.3	69.6	27	41.4	64	2 weeks	0	5
Rossi, 2014 [5]	NA	Multicenter, prospective, real-life study.	26	816	Fluticasone/salmeterol (500/50 µg bid), budesonide/formoterol (400/12 µg bid), beclometasone/formoterol (200/12 µg bid), other ICS/LABA from different inhalers.	ICS/LABA	Long-acting broncodilators.	Moderate COPD, post-bronchodilator FEV_1/FVC <88% and <89% predicted for men and women, respectively, and FEV_1 >50% predicted.	72.4	71.6	23	NA	71.4	52 weeks	<2	NA
Choudhury, 2007 [1]	NCT00440687	Randomized, double-blind, placebo-controlled.	52	260	Patient's usual medication.	Fluticasone proprionate (500 µg bid).	Placebo	COPD, post-bronchodilator FEV_1 of <80% predicted, FEV_1/FVC <70%, pre to post-bronchodilator change in FEV_1 <15%. Patients with an FEV_1 >15% but a volume change of <200 ml were also included.	67.5	52	38.1	39.4	54.1	8 years	1.90	5
Wouters, 2005 [4]	NA	Multicentre, randomized, double blind, parallel group.	52	340	Fluticasone/salmeterol (500/50 µg bid).	Fluticasone/salmeterol (500/50 µg bid)	Salmeterol (50 µg bid)	COPD, pre-bronchodilator FEV_1 30–70% of predicted, FEV_1/FVC	63.5	74	37	36.3	47.8 (pre-bronchodilator)	NA	≥2	5

Van der Valk, 2002 [3]	NA	Single center study,randomized,double-blind,parallel-group	26	244	Fluticasone proprionate (500 µg bid) plus ipratropium bromide (40 ug qid).	Fluticasone proprionate (500 µg bid)	Placebo	<88% for men and <89% for women, reversibility <10% of predicted normal $FEV_{1.}$ Moderate to severe COPD, pre-bronchodilator FEV_1 25-80% of predicted, pre-bronchodilator FEV_1/FVC <60%	64.1	84.5	27.7	37.8	56.8	4 months	1.34	4
O'Brien, 2001 [2]	NA	Randomized, double-blind, parallel-group, crossover prospective study	12	15	NA	Beclomethasone dipropionate (84 ug qid)	Placebo	Stable COPD, FEV_1 47% of the predicted volume	66.9	100	46.6	59.8	47	NA	NA	3

bid: twice a day
COPD: chronic obstructive pulmonary disease
FEV_1: forced expiratory volume in 1 second
FVC: Forced vital capacity
ICS:Inhaled corticosteroid
LABA: long-acting β_2-agonist
LAMA: long-acting muscarinic antagonists
NA: not available
PDE: phosphodiesterase
qd: once a day
qid: four times daily

Table 2. Definition of exacerbation as reported by studies included in the meta-analysis.

Study	Definition of exacerbation
Vogelmeier, 2017 [6]	Prescription of oral steroids and/or antibiotics or hospitalization.
Kunz, 2015 [8]	NA
Magnussen, 2014 (Rodriguez-Roisin, 2016) [7, 22]	A moderate exacerbation was defined as an increase in lower respiratory tract symptoms related to COPD or the new onset of two or more such symptoms, with at least one symptom lasting 3 or more days and for which the treating physician prescribed antibiotics, systemic glucocorticoids, or both. A severe exacerbation was defined as an exacerbation requiring hospitalization in an urgent care unit.
Rossi, 2014 [9]	Worsening for at least two consecutive days of two or more of the major symptoms (dyspnoea, sputum volume or sputum purulence) or worsening of any one major symptom together with any one minor symptom (sore throat, colds (nasal discharge or nasal congestion), fever without other cause, cough or wheeze). Moderate exacerbations were those managed with antibiotics and/or oral corticosteroids; severe exacerbations were those that resulted in hospitalization.
Rossi, 2014 [5]	Change in symptoms leading to a brief course of antibiotics or systemic corticosteroids or both.
Choudhury, 2007 [1]	The presence for at least two consecutive days of increase in any two 'major' symptoms or increase in one 'major' and one 'minor' symptom according to criteria modified from Anthonisen and colleagues [38].
Wouters, 2005 [4]	If the patient's condition worsened and a course of oral corticosteroid was indicated based on a clinician's judgment (standardised course of prednisolone tablets 30 mg/day for 10 days at the discretion of the physician accompanied by a 10 day course of antibiotics), the exacerbation was defined as moderate. If hospitalisation was required at the discretion of the clinician, the exacerbation was considered severe.
Van der Valk, 2002 [3]	The worsening of respiratory symptoms that required treatment with a short course of oral corticosteroids or antibiotics as judged by the study physician.
O'Brien, 2001 [2]	NA

NA: not available

COPD: chronic obstructive pulmonary disease

Table 3. GRADE evidence profile: ICS withdrawal compared to ICS continuation for COPD.

Outcomes	Quality of the evidence (GRADE)	Risk difference with ICS withdrawal
Number of exacerbations	□□□□ HIGH	45 more per 1000 (18 fewer to 117 more)
Change in FEV_1	□□□□ HIGH [a]	30 ml lower (43 lower to 18 lower)
Change in SGRQ	□□□□ HIGH [b]	1.33 units higher (0.27 higher to 2.39 higher)

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different)
Low quality: our confidence in the effect estimate is limited (the true effect may be substantially different from the estimate of the effect)
Very low quality: we have very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of effect)

a. I^2 79%
b. OIS not reached
CI: Confidence interval; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroid; OIS: Optimal Information Size
SGRQ: Saint George's Respiratory Questionnaire

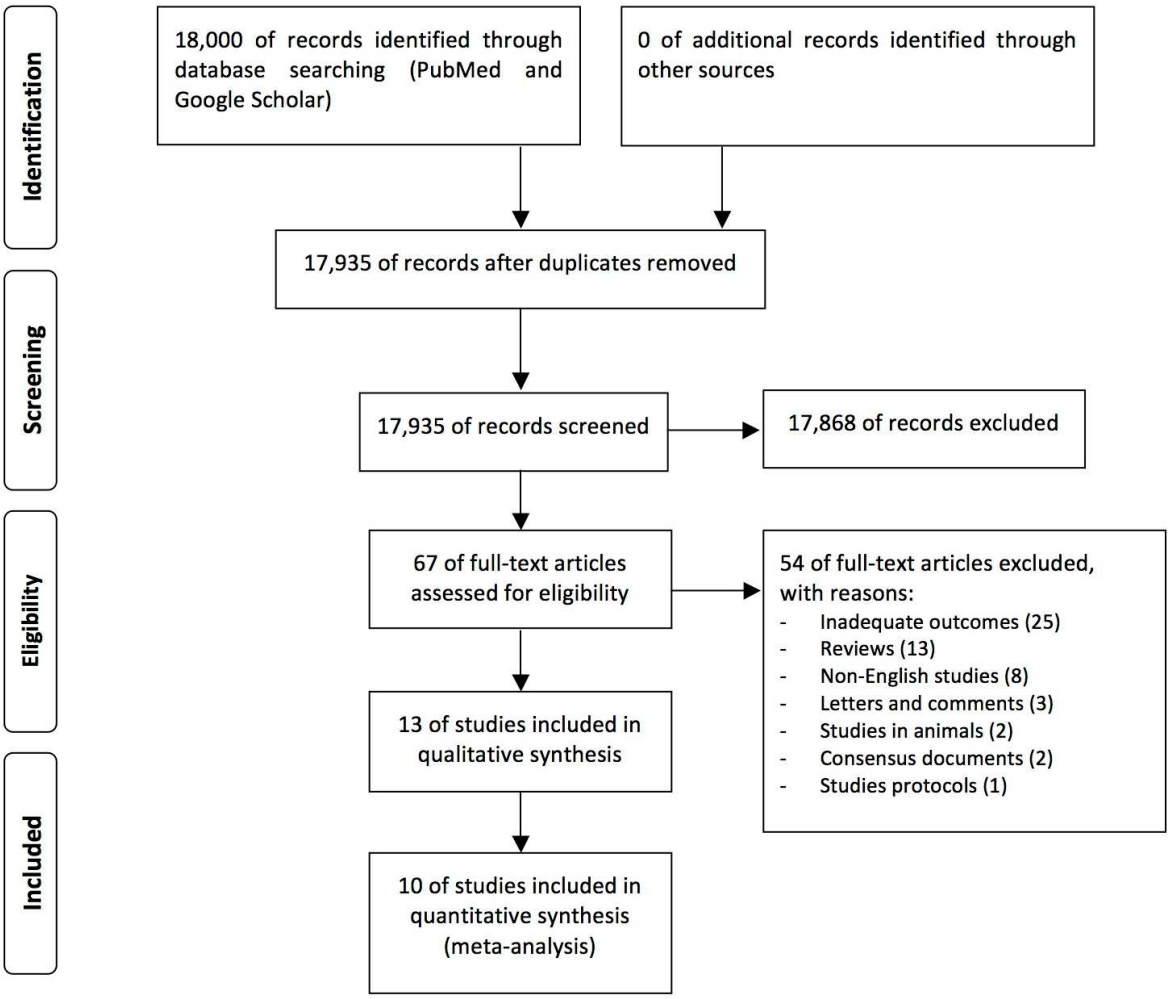
Figure legends

Figure 1. PRISMA flow diagram for the identification of studies included in the meta-analysis concerning the impact of impact of inhaled corticosteroid withdrawal in chronic obstructive pulmonary disease.

Figure 2. Impact of ICS withdrawal vs. continuation on the risk of COPD exacerbations (A), change in FEV_1 (B), and SGRQ (C). *** P<0.001 and * P<0.05. CI: confidence interval; FEV_1: forced expiratory volume in one second; ICS: inhaled corticosteroid; RCT: randomized clinical trial; SMD: standardized mean difference; SGRQ: St. George's Respiratory Questionnaire.

Figure 3. Impact of ICS withdrawal vs. continuation on the risk of experiencing at least one COPD exacerbations (A) and the time to the first exacerbation (B). * P<0.05. CI: confidence interval; COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; RCT: randomized clinical trial.

Figure 4. Publication bias assessment via Funnel plots (left panels) and Egger's test (right panels) for the impact of ICS withdrawal vs. continuation on the risk of COPD exacerbations (A and B), change in FEV_1 (C and D), and SGRQ (E and F). COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in one second; ICS: inhaled corticosteroid; SGRQ: St. George's Respiratory Questionnaire; SND: standard normal deviate.


Identification
Screening
Eligibility
Included
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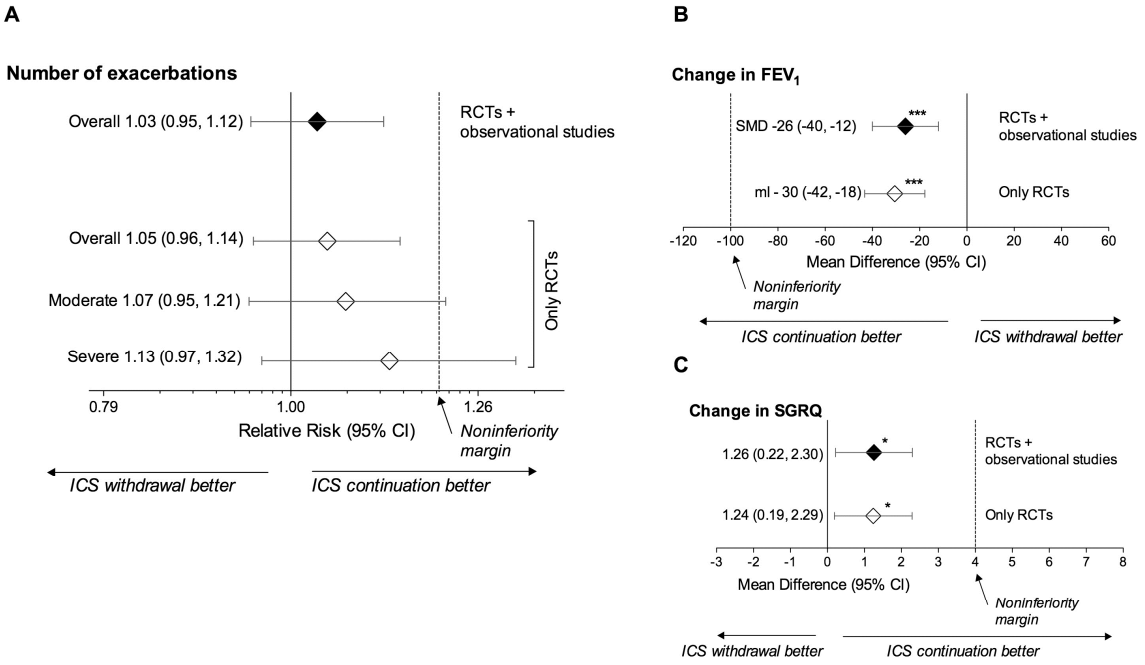
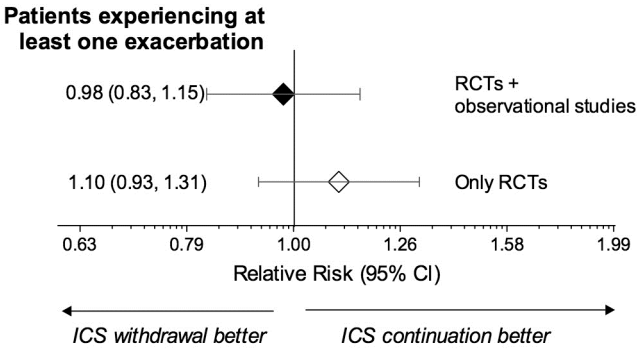
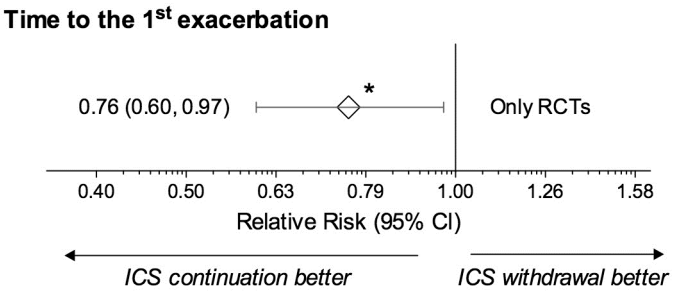
0 of additional records identified through other sources
17,935 of records after duplicates removed
17,935 of records screened
17,868 of records excluded
67 of full-text articles assessed for eligibility
54 of full-text articles excluded, with reasons:
- Inadequate outcomes (25)
- Reviews (13)
- Non-English studies (8)
- Letters and comments (3)
- Studies in animals (2)
- Consensus documents (2)
- Studies protocols (1)
13 of studies included in qualitative synthesis
10 of studies included in quantitative synthesis (meta-analysis)

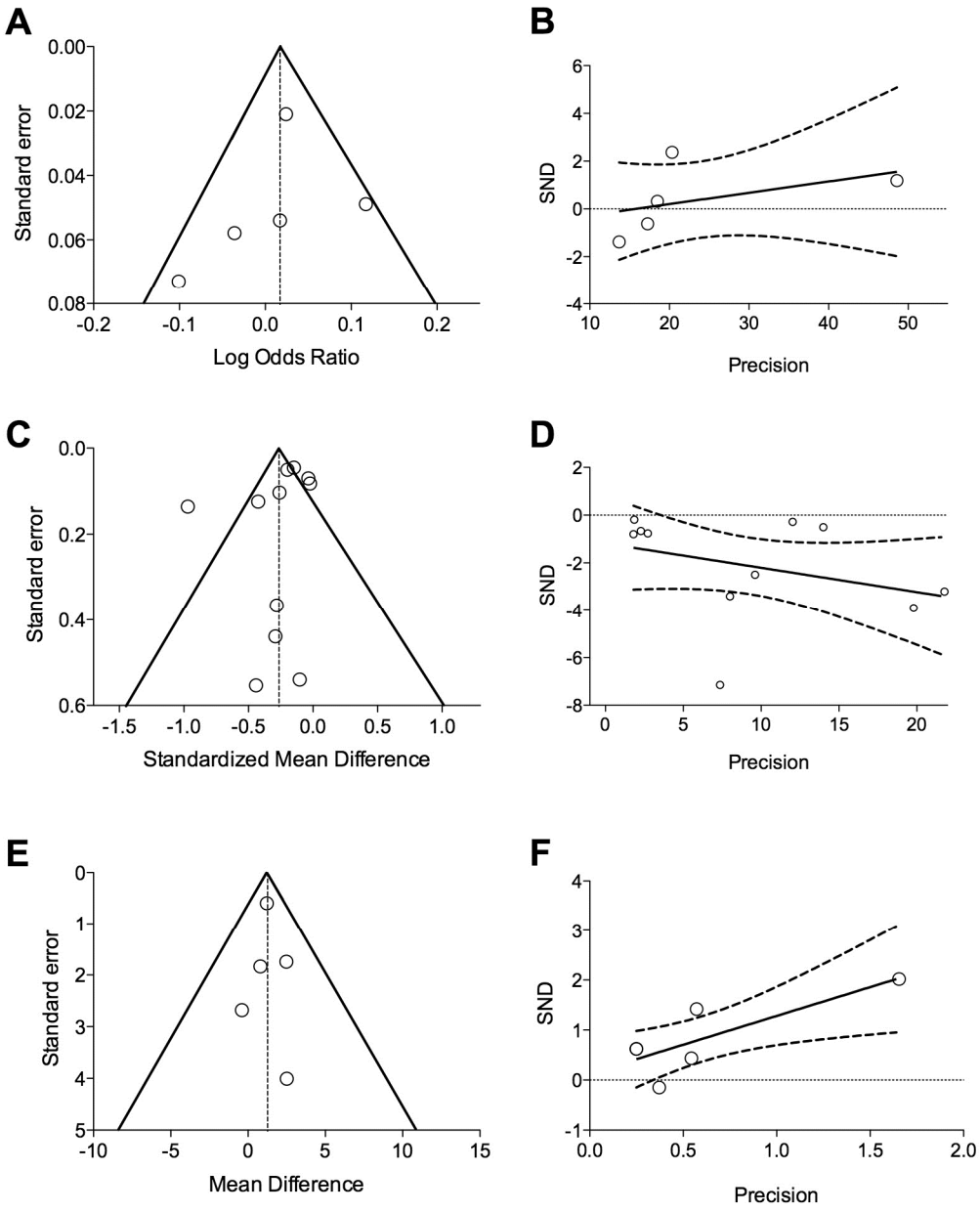


A



B




A
Standard error
0.00
0.02
0.04
0.06
0.08
-0.2
-0.1
0.0
0.1
0.2
Log Odds Ratio
B
SND
6
4
2
0
-2
-4
10
20
30
40
50
Precision
C
Standard error
0.0
0.2
0.4
0.6
-1.5
-1.0
-0.5
0.0
0.5
1.0
Standardized Mean Difference
D
SND
2
0
-2
-4
-6
-8
0
5
10
15
20
Precision
E
Standard error
0
1
2
3
4
5
-10
-5
0
5
10
15
Mean Difference
F
SND
4
3
2
1
0
-1
0.0
0.5
1.0
1.5
2.0
Precision