Systematic review on long-term adverse effects of inhaled corticosteroids in the treatment of COPD

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Abstract

Inhaled corticosteroids (ICSs) are indicated for the prevention of exacerbations in COPD; however, a significant proportion of patients at low risk of exacerbations are treated with ICSs. We conducted a systematic review including a diversity of types of study designs and safety outcomes with the objective of describing the risk of adverse effects associated with the long-term use of ICSs in patients with COPD.

A total of 90 references corresponding to 83 studies were included, including 26 randomised clinical trials (RCTs), 33 cohort studies, and 24 nested case–control (NCC) studies. Analysis of 19 RCTs showed that exposure to ICSs for ⩾1 year increased the risk of pneumonia by 41% (risk ratio 1.41, 95% CI 1.23–1.61). Additionally, cohort and NCC studies showed an association between ICSs and risk of tuberculosis and mycobacterial disease. There was a strong association between ICS use and local disorders such as oral candidiasis and dysphonia. The association between ICSs and the risk of diabetes and fractures was less clear and appeared significant only at high doses of ICSs.

Since most patients with COPD are elderly and with frequent comorbidities, an adequate risk–benefit balance is crucial for the indication of ICSs.

Introduction

Inhaled corticosteroids (ICSs) combined with long-acting bronchodilators are indicated for patients with COPD who experience exacerbations despite treatment with long-acting β_2-agonists (LABAs) and long-acting antimuscarinic agents (LAMAs) [1]. Furthermore, recent studies have shown that the efficacy of ICSs in the prevention of exacerbations is higher in patients with high concentrations of blood eosinophils, but very limited in patients with blood eosinophil levels below 100 cells·μL^{-1} [2, 3]. Despite these indications, studies in different countries have demonstrated excessive and inadequate use of ICS in patients with mild or moderate COPD who are at low risk of exacerbations [4–6].

The development of inhaled forms of corticosteroids for respiratory diseases, initially asthma and later COPD, represented a great advance, because they opened up the possibility of adequately treating these diseases with lower doses of corticosteroids and with significant reductions in systemic exposure to the drug. However, there is some systemic absorption of ICSs [7], and due to the prolonged life expectancy of patients with COPD, patients can be exposed to the drug for decades, with possible risks of long-term corticosteroid-related side-effects. This is particularly important in COPD, because the population affected

is usually older individuals with frequent comorbidities, such as type 2 diabetes mellitus and mycobacterial infections, among others, which may be susceptible to being aggravated by corticosteroids [8].

The large randomised clinical trials (RCTs) conducted at the beginning of the century revealed an increased risk of nonfatal pneumonia associated with the use of ICSs in COPD [9]. In addition, several studies observed a relationship between ICSs and local disorders such as oral candidiasis and dysphonia [10]; however, other less frequent side-effects may require larger populations exposed for longer periods of time to be identified.

We undertook the following analysis with the objectives of identifying and describing studies reporting the risks of adverse events associated with long-term use of ICSs in adult patients with COPD and estimating these risks.

Methods

Design and selection criteria

We conducted a systematic review with a broad focus, including a diversity of types of study designs and safety outcomes. Studies were included that met the following criteria for study design, population, intervention and outcomes: 1) RCTs, observational controlled studies (prospective or retrospective cohort studies, nested case–control studies (NCCs) and single cohort studies (if the sample was >500 participants); 2) adult patients diagnosed with COPD (if the study included a mixed population, specific data for patients with COPD should be available); 3) studies reporting data on safety outcomes in patients exposed to long-term use (defined as at least a 1-year period of continuous treatment) of ICSs alone or in combination; 4) studies reporting the rate (or the odds for case–control studies) of at least one of the following safety outcome measures: pneumonia, mycobacterium infections (tuberculosis (TB) and nontuberculous mycobacteria (NTM)), sepsis, osteoporosis, bone fractures, diabetes mellitus (new-onset, progression and/or switch from oral medication to insulin), glaucoma, cataract, hypertension, adrenal insufficiency, dysphonia and oral candidiasis.

The study was registered in Prospero (CRD42020168023) in April 2020.

Search strategy and study selection

For the electronic search, we designed a specific algorithm for MEDLINE and EMBASE (supplementary table S1). In addition, we performed a search for other reviews, either systematic or narrative, on the safety of ICSs and manually reviewed all the references included. The Covidence® software was used to manage the bibliography retrieved from the search across all the review process. Three authors (A. Auladell-Rispau, J. Mohammed and G. Urrútia), working in pairs, screened the search results based on the title and abstract independently. A full-text copy of each eligible reference was retrieved and the same researchers independently confirmed eligibility based on the inclusion criteria. Disagreements were discussed and solved by consensus.

Data extraction

The same authors extracted all relevant data on the main characteristics (design and methods, study population and intervention) and results of the selected studies.

Data analysis

Since the review includes several study designs that cannot be combined in a meta-analysis, the results are presented separately for each type of study design. Whenever possible, a meta-analysis was performed separately for RCTs and cohort studies, providing that these studies reported a measure of comparative effects such as hazard ratios (HR) or risk ratios (RR). Data are displayed using forest plots. We examined between-study heterogeneity using the I^2 statistic. The quality of the clinical trials included in the meta-analyses was evaluated with the Cochrane risk of bias assessment tool [11]. When studies performed comparisons using ICSs in both study groups, results (rates) were reported narratively. Likewise, in NCC studies, in which the measure of association was the odds ratio (OR), the results are presented narratively.

Results

Our search in MEDLINE through PubMed yielded a total of 2711 bibliographic references, and the search in EMBASE provided 4287 references; both searches included references published up to 20 October 2020. An additional search was performed to identify other reviews related to this topic and included a total of 240 references. The search results, as well as the decisions made during the eligibility process, are shown in a PRISMA flowchart (supplementary figure S1). A total of 90 references from 83 studies were included in the review, corresponding to 26 RCTs [9, 12–43], 33 cohort studies [44–76] and 24 NCC

studies [77–100]. A complete description of these studies is provided in supplementary table S2. Safety outcomes have been grouped into four main categories according to the nature of the events: infectious, metabolic, local and other.

Infectious adverse events
Pneumonia
In total, 47 studies reported this outcome (19 RCTs, 20 cohort studies and eight NCC studies). The pooled analysis of 19 RCTs with 66 485 participants showed that exposure to ICSs for ⩾1 year increased the risk of pneumonia by 41% (RR 1.41, 95% CI 1.23–1.61; p<0.00001; I^2=55%) [9, 12–14, 16, 19, 22, 23, 25, 26, 29, 30, 33–39] (figure 1). An interaction was found between the risk of pneumonia and the type of ICS used, with the highest risk being associated with fluticasone (10 studies with 45 870 participants) [9, 12–14, 16, 23, 25, 26, 30, 39]. A similar trend was observed with beclometasone (two studies with 4221 participants) [33, 38] and mometasone (one study with 911 participants) [22], but the low number of available studies limited the statistical power of the analysis and, therefore, resulted in a low-precision estimate. Conversely, exposure to budesonide (six studies with 13 479 participants) [19, 29, 34–37] was not associated with an increased risk of pneumonia, although a high heterogeneity was observed due to a recent large study which observed an increased risk [34]. Of the 21 cohort studies that reported this outcome, 16 described the effects in terms of HR and could be meta-analysed [46, 47, 49, 50, 53, 54, 57–59, 61, 66–69, 73, 74]. Exposure to ICSs for ⩾1 year increased the risk of pneumonia by 26% (HR 1.26, 95% CI 1.14–1.38, p=0.0001; I^2=93%) (supplementary figure S2).

The remaining studies which were not suitable for the meta-analysis are summarised in table 1. Of these, only one study compared ICS use with no ICS use [71], while the remaining studies used ICSs in both study arms and, therefore, only provided descriptive frequency data. Incidence rates were highly variable among studies, and the risk of pneumonia in patients receiving fluticasone seemed to be higher than in patients receiving budesonide [52, 72], although one other study did not show this association [55]. According to one study (that was included in the meta-analysis), the risk of pneumonia was associated with higher doses of ICSs and the effects of ICSs were only significant in patients with forced expiratory volume in 1 s (FEV_1) ⩾50% [53].

The results of eight NCC studies are summarised in table 2 [80, 81, 88, 92, 96, 97, 99, 100]. Overall, they confirm the association between ICS exposure and the risk of pneumonia. Higher doses of ICSs, current use of ICSs and exposure to fluticasone were also found to be associated with a higher risk of pneumonia.

TB and NTM
Nine studies reported this outcome: five cohort studies [56, 65, 71, 75, 76] and four NCC studies [77–79, 90]. None of these studies were suitable for a meta-analysis. Overall, the cohort studies found that the use of ICSs was associated with the risk of developing TB, especially for patients receiving high ICS doses and with a history of previous pulmonary TB [56, 65, 75]. Only one study did not find this association [71]. According to one study, long-term treatment with budesonide was associated with rates of TB similar to those with fluticasone [76]. Two NCC studies observed an association between ICS exposure and pulmonary TB [78, 90] and two others associated ICSs with NTM [77, 79] (tables 1 and 2).

Sepsis
Only one cohort [70] and one NCC study [82] related to the development of sepsis were identified. The cohort study compared the effect of budesonide and fluticasone on the risk of sepsis in patients with COPD and found incidence rates of sepsis of 4.99 and 5.74 per 100 person-years, respectively. Fluticasone was associated with a higher risk of sepsis (adjusted HR (aHR) 1.15, 95% CI 1.07–1.24) and septic shock (aHR 1.14, 95% CI 1.01–1.29) compared with budesonide [70].

The NCC study included 163 514 patients treated for COPD, 1704 of whom were hospitalised or died with sepsis during follow-up (incidence rate 1.94 per 1000 per year). The risk of sepsis was not increased with ICS, even at high doses, while the risk was increased with oral corticosteroids [82].

Metabolic adverse events
Osteoporosis
In total, 12 studies reported this outcome (eight RCTs, two cohort studies and one case–control study). The reporting methods for bone mineral density (BMD) data in the RCTs precluded pooling results in a meta-analysis [9, 21, 28, 29, 31, 32, 35, 42]. In one study, BMDs of the lumbar spine (p=0.007) and the femoral neck (p<0.001) were significantly lower in the ICS group (triamcinolone) versus placebo after 3 years [42]. Another study showed small but statistically significant differences in changes from baseline
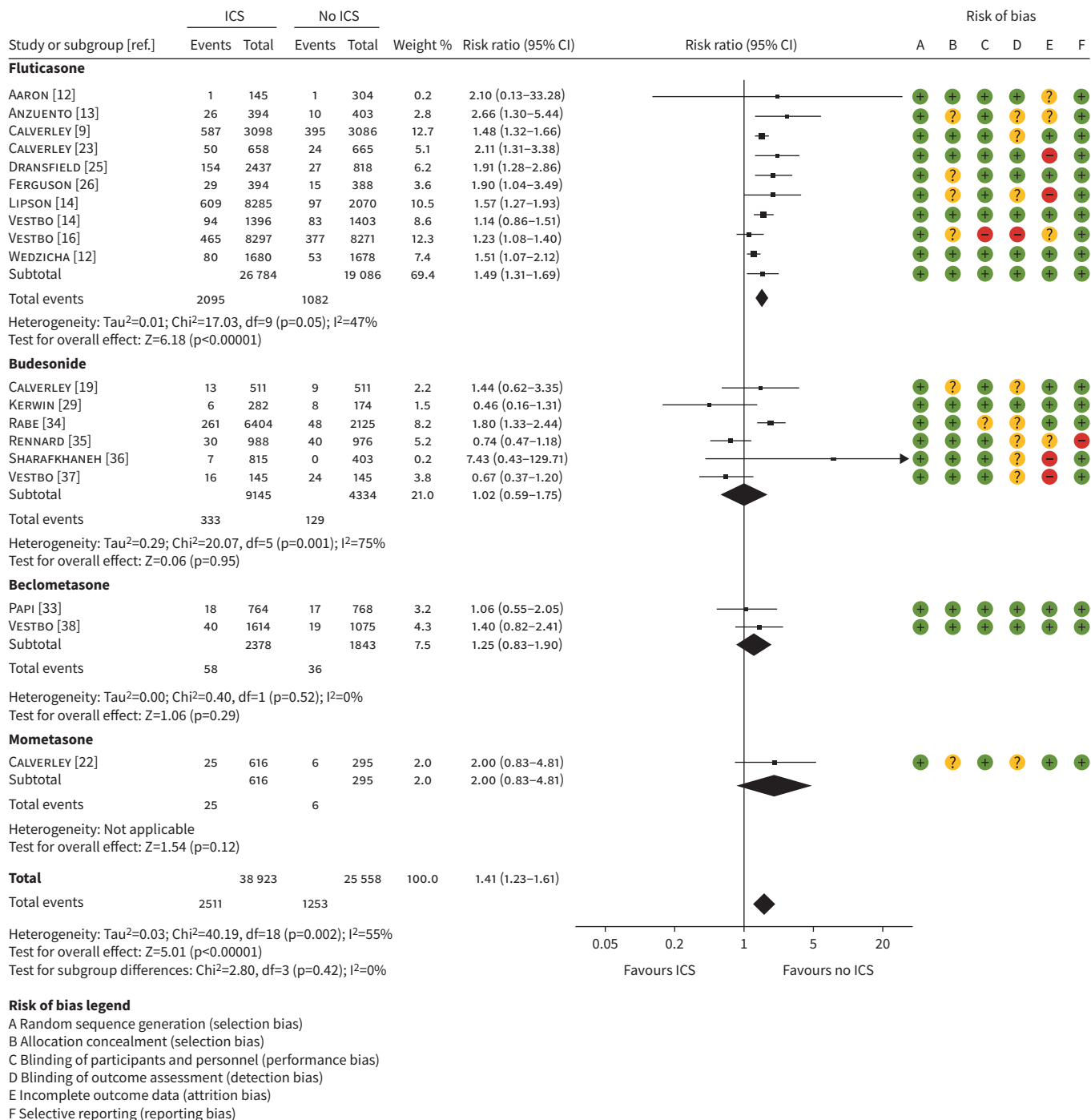
FIGURE 1 Pooled risk ratios for pneumonia (Mantel-Haenszel, random-effects model). ICS: inhaled corticosteroid.

for budesonide 320 µg compared with all other treatments for total lumbar spine BMD (p⩽0.037) and for budesonide 320 µg *versus* formoterol for total hip BMD (p=0.012) [35]. However, the remaining six RCTs did not find such an effect [9, 21, 28, 29, 31, 32].

In addition, two cohort studies reported a significant BMD decline with ICS use [60], and an evident dose–response relationship with increased risk of osteoporosis at mean ICS exposures of 500 µg·day^{-1} or greater [62]. Finally, one NCC found that long-term use of ICSs was associated with osteoporosis in multivariate regression analysis (HR 0.70, 95% CI 0.59–0.83; p<0.0001) [91].

TABLE 1 Outcomes from cohort studies (not suitable for meta-analysis)

First author [ref.]	Results	Conclusions
Infectious complications: pneumonia		
Cohort studies with no ICS use in control group		
Wu [71]	Pneumonia event rate with ICS use: 703/8813 (8.0%) Pneumonia event rate with no ICS use: 1654/35 252 (4.7%)	The aim of the study was to explore the association between post-ICS pulmonary infections (pneumonia and TB) and lung cancer. The incidence observed in those exposed to ICSs was substantially higher than in those not exposed.
Cohort studies with ICS use in both study arms		

YANG [72]	Pneumonia:
	    Event rate for fluticasone/salmeterol: 12.11 per 100 person-years
	    Event rate for budesonide/formoterol: 10.65 per 100 person-years
	    aHR 1.13 (95% CI 1.08–1.20)
	Pneumonia requiring mechanical ventilation:
	    Event rate for fluticasone/salmeterol: 3.94 per 100 person-years
	    Event rate for budesonide/formoterol: 3.47 per 100 person-years
	    aHR 1.14 (95% CI 1.05–1.24)
		Patients receiving fluticasone/salmeterol had a higher incidence rate and a higher risk of pneumonia than patients receiving budesonide/formoterol (13% increase of risk).
		
		Patients receiving fluticasone/salmeterol had a higher incidence rate and a higher risk of pneumonia requiring mechanical ventilation than patients receiving budesonide/formoterol (14% increase of risk).

JANSON [52]	Pneumonia event rate for fluticasone/salmeterol: 11.0 per 100 patient-years Pneumonia event rate for budesonide/formoterol: 6.4 per 100 patient-years RR 1.73 (95% CI 1.57–1.90; p<0.001)	The observed risk with fluticasone/salmeterol was greater than with budesonide/formoterol (73% increase of risk).
KERN [55]	Pneumonia event rate for fluticasone/salmeterol: 702/3697 (19.0%) Pneumonia event rate for budesonide/formoterol: 634/3697 (17.2%) OR 0.92 (95% CI 0.81–1.04)	The proportion of patients diagnosed with pneumonia was similar in each group. No evidence of an association was observed.

JANSON [53]	The highest risk of pneumonia was associated with a high- *vs* low-dose of ICSs (HR 1.41, 95% CI 1.23–1.62)
	The risk of pneumonia was significantly increased with ICSs in patients with FEV_1 ⩾50% but not in those with FEV_1 <50%, with both low- and high-dose ICS use:
	    Low-dose ICS *vs* no ICS: if FEV_1 <50%, HR 1.06 (95% CI 0.91–1.25), and if FEV_1 ⩾50%, HR 1.20 (95% CI 1.05–1.38)
	    High-dose ICS *vs* no use: if FEV_1 <50%, HR 0.98 (95% CI 0.81–1.17), and if FEV_1 ⩾50, HR 1.31 (95% CI 1.10–1.56)
		ICS use increased the risk of pneumonia in patients with COPD. Asthma was an independent risk factor for pneumonia in the COPD population. Multivariate analysis identified independent predictors of pneumonia in the overall population. The highest risk of pneumonia was associated with high-dose ICS.

Infectious complications: TB and NTM lung disease		

KIM [56]	The study assessed the risk of TB in patients with COPD depending on ICS use and the presence of a TB scar at baseline:
	    ICS use with TB scar: HR 26.9 (95% CI 3.36–215.75; p=0.002)
	    ICS use without TB scar: HR 9.88 (95% CI 1.11–87.93; p=0.04)
	    No ICSs with TB scar: HR 3.85 (95% CI 0.35–42.55; p=0.272)
	    No ICSs without TB scar: reference group
		The use of ICSs was strongly associated with the risk of developing TB. The highest risk was observed in patients who were ICS users and had previous TB lesions.

SHU [65]	This prospective cohort study assessed the risk of developing active TB during follow-up according to the use and dose of ICS:
	    High-dose ICS: 5/50
	    Medium-dose ICS: 2/72
	    No ICS: 3/238 (p=0.010)
		The use of high-dose ICSs and prior pulmonary TB were associated with an increased risk of pulmonary TB in patients with COPD.

LEE [75]	Univariate time-dependent Cox regression analysis in 23 594 patients with COPD revealed that ICS dose-dependently increased the risk of pulmonary TB (HR 1.01, 95% CI 1.00–1.02); in multivariate analysis, the effect of ICSs became obscured; adding ICSs into the multivariate model produced a minimal effect on the other co-variables (HR 1.01, 95% CI 0.99–1.03)	Although ICS therapy has been shown to predispose patients with COPD to pneumonia in large RCTs, it does not increase the risk of TB in real-world practice.

Continued

TABLE 1 Continued		
First author [ref.]	Results	Conclusions
Wu [71]	TB event rate for ICS use: 182/8813 (2.1%) TB event rate for no ICS use: 678/35 252 (1.9%)	The aim of the study was to explore the association between post-ICS pulmonary infections (pneumonia and TB) and lung cancer. The incidence of TB observed in those exposed to ICSs was similar to that in those not exposed.
HUANG [76]	Fluticasone/salmeterol cohort: incidence rate 0.15/100 person-years Budesonide/formoterol cohort: incidence rate 0.17/100 person-years aHR 0.900 (95% CI 0.565–1.435)	Long-term treatment with budesonide/formoterol was associated with rates of TB similar to those of fluticasone/ salmeterol in patients with COPD.
Metabolic complications: fractures		

CHO [46]	In patients with severe COPD:
	   ICSs alone: 22/169 (13%); rate 53.8 per 1000 patient-years
	   ICS/LABAs: 28/638 (4.4%); rate 24.1 per 1000 patient-years
	 In patients with non-severe COPD:
	   ICSs alone: 38/277 (13.7%); rate 25.1 per 1000 patient-years
	   ICS/LABAs: 70/911 (7.7%); rate 12.4 per 1000 patient-years
	 Cumulative hazards during study period and 5-year cumulative hazards of fracture:
	   New ICS users: 0.150 and 0.084
	   New ICS/LABA users: 0.120 and 0.045 (p<0.001)
		Among newly diagnosed patients with COPD and new users of ICSs or ICS/LABA, use of ICS/LABA in a single inhaler was associated with delayed first hospitalisation for fracture, as compared with use of ICSs alone.

GONNELLI [51]	Prevalence of vertebral fractures (radiology):
	   No treatment (n=509): 32.3%
	   ICS (n=1664): 42.6%
	   Other treatments (n=449): 41.8%
	 Prevalence of vertebral fractures (radiology) in patients with ICSs (n=1664) by dose:
	   ICS ⩽750 g: 39.9%
	   ICS 750–1500 µg: 41.9%
	   ICS >1500 µg: 46%
	 Fractures vs no fractures:
	   ICS >1500 µg·day^{-1}: OR 1.40 (95% CI 1.04–1.89; p 0.03)
	   ICS 750–1500 µg·day^{-1}: OR 1.36 (95% CI 0.93–1.72; NS)
	   ICS <750 µg·day^{-1}: OR 1.26 (95% CI 0.98–1.89; NS)
	   No treatment: OR 1.00 (reference group)
		The prevalence rates of vertebral fractures increased in patients taking higher daily doses of ICS.
		 The risk of vertebral fractures was significantly increased in patients taking the highest dose (>1500 ug) of ICS. The use of ICSs at doses ranging from 751–1500 ug was associated with a positive, but not significant, increase in vertebral fracture risk.

Metabolic complications: diabetes		

CAUGHEY [45]	Diabetes-related hospitalisations:
	   After 5 years, 19.8% of ICS users had a diabetes-related hospitalisation vs 16.2% in non-users (p=0.18)
	   When stratified by ICS dose, patients who received a total DDD of ICSs ⩾0.83/day had a 94% increased likelihood of diabetes-related hospitalisation (HR 1.94, 95% CI 1.14–3.28; p=0.014) compared with patients not receiving ICS; lower ICS doses (<0.83 DDD/day) not associated with increased risks of diabetes-related hospitalisations
		In patients with diabetes and COPD, an increased risk of diabetes-related hospitalisations was only evident with the use of high doses of ICS. A dose-dependent increase in risk associated with ICS use was observed.

FLYNN [49]	Worsening of existing diabetes:
	   ICS use: 326.1 per 1000 person-years
	   No ICS use: 318.4 per 1000 person-years
	   HR 0.57 (95% CI 0.25–1.30)
		ICS use was not associated with new-onset diabetes nor worsening of existing diabetes.

PRICE [63]	Change in HbA1c:
	   ICS use: median 0.18% (IQR −0.23–0.6%)
	   No ICS use: median 0.03% (IQR −0.33–0.5%)
	   Adjusted difference 0.16% (95% CI 0.05–0.27%)
	 Increase in rate of hospitalisation for diabetes mellitus:
	   ICS use: 41 (6.0%)
	   No ICS use: 31 (4.5%)
	 Progression to insulin:
	   ICS use: 28 (4.7%)
	   No ICS use: 12 (2%)
		For patients with COPD and comorbid type 2 diabetes mellitus, ICS therapy may have a negative impact on diabetes control. Patients prescribed higher cumulative doses of ICSs may be at greater risk of diabetes progression.

TABLE 1 Continued		
First author [ref.]	Results	Conclusions
PRICE [62]	Diabetes progression: Patients initiating ICS: mean rate 33.3 per 100 patient-years Control (LABD): mean rate 37.2 per 100 patient-years HR 1.04 (95% CI 0.87–1.25) Diabetes onset: Patients initiating ICS: mean rate 1.25 diagnoses per 100 patient-years Control (LABD): mean rate 1.05 diagnoses per 100 patient-years aHR 1.27 (95% CI 1.07–1.50; p=0.006)	For patients prescribed ICS, compared with LABD, the risk of diabetes onset was significantly increased with overall no increase in risk of diabetes progression. The risk of diabetes progression also showed a clear dose–response relationship with mean daily ICS exposure for all patients and for the GOLD A/B and GOLD C/D subgroups.
AJMERA [44]	New-onset diabetes: ICS use: 7.4% No ICS use: 1.39% aOR 1.23 (95% CI 1.07–1.47)	ICS use was associated with an increased risk of new-onset diabetes.
Local complications: eye disorders		
FLYNN [49]	Cataract-related outcomes: cumulative exposure univariate analysis HR 1.43 (95% CI 1.11–1.83); multivariate analysis HR 1.42 (95% CI 1.07–1.88)	There was a significant association between ICS use and increased cataract-related admissions.
KENDZERSKA [54]	Cataract surgery: adjusted association, HR 0.93 (95% CI 0.88–0.98)	No association between ICS use and cataract surgery.
Local complications: oral candidiasis		
DEKHUIJZEN [48]	Oral candidiasis: ICS/LABA: 5.5% No ICS: 2.7% aOR 2.18 (95% CI 1.84–2.59) Comparison between type of ICS: Budesonide: 5.7% Fluticasone: 7.0% aOR 0.77 (95% CI 0.63–0.94) After adjusting for intended ICS daily dose: fully aOR 1.04 (95% CI 0.54–2.00)	ICS use increases the incidence of oral thrush in COPD, and this effect is dose-dependent for fluticasone/salmeterol therapies. Significantly fewer patients prescribed budesonide developed oral thrush compared with patients prescribed fluticasone. However, after adjusting for intended ICS daily dose, no significant differences were found in the incidence of oral thrush between budesonide and fluticasone study arms. A pattern of increasing odds for oral thrush with increasing ICS dose was observed.

ICS: inhaled corticosteroid; TB: tuberculosis; aHR: adjusted hazard ratio; RR: risk ratio; OR: odds ratio; HR: hazard ratio; FEV$_1$: forced expiratory volume in 1 s; NTM: nontuberculous mycobacteria; RCT: randomised clinical trial; LABA: long-acting β$_2$-agonist; NS: nonsignificant; DDD: defined daily dose; GOLD: Global Initiative for Chronic Obstructive Lung Disease; aOR: adjusted odds ratio; IQR: interquartile range; LABD: long-acting bronchodilators.

Fractures

In total, 19 studies reported this outcome: nine RCTs, five cohort studies and five NCC studies. The pooled analysis of 10 RCTs with 41 342 participants did not observe a higher risk of fracture with exposure to ICSs (RR 1.10, 95% CI 0.97–1.25; p=0.13; I^2=0%) [9, 14, 16, 18, 24, 25, 27, 31, 34, 43] (figure 2). No differences were observed depending on the type of ICS used; however, this analysis is not very informative since all but two studies used fluticasone [27, 34].

Five cohort studies reported this outcome [46, 49–51, 54]; of these, only three compared ICSs versus no ICSs and reported the effects in terms of HRs. These studies did not find an increased risk of fractures in patients exposed to ICSs for ⩾1 year (HR 1.00, 95% CI 0.97–1.03, p=0.79; I^2=0%) [49, 50, 54] (supplementary figure S3). Two additional cohort studies reported on fractures, but as they lacked a control group without ICS use, the results are presented in a descriptive way (rates) in table 1 [46, 51]. Four out of the five NCC studies showed an increased risk for fractures with ICS use [84, 89, 93, 95], with two showing an increasing risk with increased doses of ICSs [84, 95] and one found an increased risk only with fluticasone [93]. The remaining study only evaluated ICS exposure for up to 1 year and found no increased risk of nonvertebral fracture, but it could not evaluate long-term ICS use, very high ICS doses or vertebral fractures [87] (table 2).

Diabetes

The pooled analysis of four RCTs with 31 151 participants showed that long-term exposure to ICSs was not associated with an increased risk of diabetes (RR 1.10, 95% CI 0.96–1.26; p=0.15; I^2=0%) [14, 16, 25, 34] (figure 3). However, four additional cohort studies found that exposure to ICSs for ⩾1 year marginally

TABLE 2 Outcomes from nested case–control studies

First author [ref.]	Results	Conclusions
Infectious complications: pneumonia		
CASCINI [80]	Incidence rate for current ICS use: 87/1000 patient-years Incidence rate for past ICS use: 32/1000 patient-years aRR (current ICS use *vs* no use): 2.29 (95% CI 1.99–2.63) aRR (past ICS use *vs* no use): 1.23 (95% CI 1.07–1.42) In current ICS users, a dose-related trend was tested	ICS use was associated with an excess risk of pneumonia. The effect was greatest for higher doses and elderly patients.
ERNST [81]	aRR of hospitalisation for pneumonia (current ICS use *vs* no use): 1.70 (95% CI 1.63–1.77) aRR of pneumonia hospitalisation followed by death within 30 days (current ICS use *vs* no use): 1.53 (95% CI 1.30–1.80) RR of hospitalisation for pneumonia (highest doses of ICSs *vs* non-users): 2.25 (95% CI 2.07–2.44) The risk of pneumonia increased with higher ICS doses	The use of ICSs is associated with an excess risk of pneumonia hospitalisation and of pneumonia hospitalisation followed by death within 30 days among elderly patients with COPD.
JOO [88]	aOR of pneumonia hospitalisation (current ICS users *vs* non-users): 1.38 (95% CI 1.31–1.45)	The use of ICSs among patients with newly diagnosed COPD is associated with an increased risk of hospitalisation for pneumonia.
MAPEL [92]	Relative to patients using SABDs, the control group, the only treatment associated with a nonsignificant increased risk of pneumonia was ICSs used alone (OR 1.29, 95% CI 0.96–1.73; p=0.09) Users of FSC had no increased risk for pneumonia relative to SABDs (OR 1.03, 95% CI 0.74–1.42)	Patients with COPD using ICSs alone had a slightly increased risk of pneumonia that did not reach statistical significance (adjusted risk 26–29%). Those who used FSC or other combinations of ICSs with LABA did not have an increased risk for pneumonia.
SUISSA [96]	RR of serious pneumonia (current ICS use *vs* no use): 1.69 (95% CI 1.63–1.75) RR of serious pneumonia with fluticasone: 2.01 (95% CI 1.93–2.10) RR of serious pneumonia with budesonide: 1.17 (95% CI 1.09–1.26) The risk of serious pneumonia was sustained with long-term ICS use and declined gradually after stopping ICS use, disappearing after 6 months The rate of serious pneumonia was higher with fluticasone (RR 2.01, 95% CI 1.93–2.10), but was much lower with budesonide (RR 1.17, 95% CI 1.09–1.26)	ICS use by patients with COPD increases the risk of serious pneumonia. The risk is particularly elevated and dose-related to fluticasone.
SUISSA [97]	Incidence rate of serious pneumonia: 2.8/100 person-years aRR of serious pneumonia (discontinued use *vs* current use): 0.63 (0.60–0.66) Discontinuation of ICSs was associated with a decrease in the rate of serious pneumonia; the risk reduction was rapidly evident, increasing from 20% in the first month to 50% by the fourth month after discontinuation	The study assessed the effect of ICSs discontinuation in COPD on the incidence of serious pneumonia. Discontinuation of ICS use in COPD is associated with a reduction in the elevated risk of serious pneumonia, particularly with fluticasone.
THORNTON SNIDER [99]	Pneumonia (current ICS users *vs* non-users): OR 1.26 (95% CI 1.16–1.36) Pneumonia (current high-dose users *vs* non-users): OR 1.55 (95% CI 1.25–1.92) The risk increased with higher ICS doses	ICS use, particularly current use and high-dose use, is associated with increased pneumonia risk.
WANG [100]	Pneumonia (current use of ICSs *vs* no use): aOR 1.25 (95% CI 1.20–1.30) Pneumonia (past use of ICSs *vs* no use): aOR 1.21 (95% CI 1.16–1.26) There was an increase in the OR with an increase in the average daily dosage Fluticasone users were more likely to be at a higher risk of pneumonia; in contrast, there were no statistically significant associations between the risk of pneumonia and the use of budesonide	ICSs are significantly associated with an increased risk of pneumonia in patients with COPD. The effect is prominent for fluticasone-containing ICSs but not for budesonide-containing ICSs.

First author [ref.]	Results	Conclusions
TABLE 2 Continued		
Infectious complications: TB and NTM lung disease		
ANDRÉJAK [77]	NTM: Patients with COPD *vs* no COPD: aOR 13.1 (95% CI 7.4–23.3) COPD on current ICS therapy *vs* no COPD: aOR 29.1 (95% CI 13.3–63.8) COPD and former ICS use (> 6 months) *vs* no COPD: aOR 3.8 (95% CI 0.9–16.8)	Chronic respiratory disease, particularly COPD treated with ICS therapy, is a strong risk factor for NTM-PD. The risk is highly reduced when ICSs are withdrawn. The risk of NTM disease is higher with higher doses of ICS.
BRODE [79]	NTM-PD: Current ICS use *vs* non-ICS use: aOR 1.86 (95% CI 1.60–2.15) aOR for current fluticasone use: 2.09 (95% CI 1.80–2.43) aOR for current budesonide use: 1.19 (95% CI 0.97–1.45) There was a strong dose–response relationship between incident NTM-PD and cumulative ICS dose over 1 year TB: Current ICS use *vs* non-ICS use: aOR 1.43 (95% CI 0.95–2.16)	This study suggests that ICS use is associated with an increased risk of NTM-PD but was not significant for TB.
BRASSARD [78]	TB: Any ICS use: RR 1.27 (95% CI 1.05–1.53) Current ICS use: RR 1.33 (95% CI 1.04–1.71)	Exposure to ICSs is not associated with risk of TB in the presence of OCSs but is associated with increased TB risk in non-users of OCSs.
LEE [90]	TB: aOR for ICS use: 1.20 (95% CI 1.08–1.34) The association was dose-dependent (p for trend <0.001)	ICS use increases the risk of TB. A subgroup analysis revealed that ICS use increased the risk of TB development among non-users of OCSs but not among OCS users.
Metabolic complications: fractures		
GONZALEZ [84]	Fracture RR (any use of ICSs *vs* no use): 1.00 (95% CI 0.97–1.03) The fracture rate was increased with >4 years of ICS use at daily doses ⩾1000 µg in fluticasone equivalents (RR 1.10, 95% CI 1.02–1.19)	Long-term ICS use at high doses is associated with a modest increase in the risk of hip and upper extremity fractures in patients with COPD. This dose-duration risk increase does not appear to be higher for women.
JOHANNES [87]	ORs for exposure in the preceding 30 days were 1.05 (95% CI 0.89–1.24), 1.13 (95% CI 0.90–1.40), and 0.97 (95% CI 0.78–1.21) for all ICS, fluticasone propionate and other ICS, respectively No dose–response effect was present	No increased nonvertebral fracture risk with ICS exposure as a class or with fluticasone propionate alone was detected. This study could not evaluate very high-dose ICS, long-term ICS exposure or vertebral fracture risk.
LEE [89]	Exposure to ICSs at any time during follow-up was not associated with an increased fracture risk (aOR 0.97, 95% CI 0.84–1.11); however, current high-dose ICS users (⩾700 µg per day) had an increased risk of fractures compared with patients with no exposure (aOR 1.68, 95% CI 1.10–2.57)	In patients with COPD, current use of high-dose ICS was associated with an increased risk of nonvertebral fractures.
MILLER [93]	Use of FSC in the year prior to the index date was associated with a statistically significant increase in the odds of nonvertebral fractures (aOR 1.25, 95% CI 1.07–1.47)	Use of FSC was associated with an elevation in the risk of nonvertebral fractures. No increased risk was observed for other ICS use.
PUJADES-RODRÍGUEZ [95]	Risk of fracture increased with increasing mean daily doses of inhaled corticosteroid (p for trend 0.007) and was most marked in those whose daily dose was >1600 µg (OR 1.80, 95% CI 1.04–3.11)	Use of ICSs is associated with a significant increase in fracture risk, particularly at higher doses.
Metabolic complications: diabetes		
GAYLE [83]	Type 2 diabetes mellitus: The aOR for patients receiving ICSs (higher doses) significantly increased compared with patients receiving no ICS therapy (OR 1.73, 95% CI 1.65–1.82) Patients with a high number of ICS prescriptions were more likely to develop diabetes (OR 1.83, 95% CI 1.48–2.26) for 16–20 prescriptions and 1.61 (95% CI 1.53–1.69) for 1–5 prescriptions	Incidence of type 2 diabetes mellitus among patients with COPD is high and exposure to ICSs and frequent exacerbations are associated with a higher risk of type 2 diabetes mellitus among patients with COPD.

First author [ref.]	Results	Conclusions
TABLE 2 Continued		
Suissa [98]	Current use of ICSs *vs* no ICS use was associated with a 34% increase in the rate of new-onset diabetes (RR 1.34, 95% CI 1.29–1.39) and diabetes progression (RR 1.34, 95% CI 1.17–1.53) The risk increases were greatest with the highest ICSs doses, equivalent to fluticasone 1000 g per day or more (RR 1.64, 95% CI 1.52–1.76 and RR 1.54, 95% CI 1.18–2.02, respectively)	In patients with respiratory disease, ICS use is associated with modest increases in the risks of diabetes onset and diabetes progression. The risks are more pronounced at the higher doses currently prescribed in the treatment of COPD.
Local complications: eye disorders		
Jick [86]	After adjusting for age and gender, incidence rates of cataract development in the ICS subjects were slightly higher than in the nonexposed cohort (RR 1.3, 95% CI 1.1–1.5) Among individuals ⩾40 years of age, the RR increased with use of increasing numbers of ICS prescriptions; this trend was not evident in those under age 40	Age appears to modify the association between use of ICSs and the risk of cataract development with an increased effect among the oldest patients at the highest dosages of ICS. This finding may be owing to a differential effect of the drug at different ages or to the influence of diagnostic bias and uncontrolled confounding among older patients.
Gonzalez [85]	The aRR for glaucoma was 1.05 (95% CI 0.91–1.20) with ICS use in the preceding 30 days There was no dose-related effect of ICSs on the risk of glaucoma or raised intra-ocular pressure requiring treatment; continuous use of high-dose ICSs for ⩾3 months was not associated with an increased risk of glaucoma	Current use and continuous use of high-dose ICSs did not result in an increased risk of glaucoma or raised intra-ocular pressure requiring treatment.
Miller [94]	2941 incident cataract cases and 327 incident glaucoma cases were identified in the COPD cohort (n=53 191) Fluticasone (as fixed-dose combination) or ICS prescriptions were not associated with risk of incident cataracts or glaucoma for any exposure (dose) category, after adjusting for confounders A trend was observed according to the duration and the number of prescriptions in the last year for cataracts, but not for glaucoma	FSC or other ICS exposure was not associated with an increased odds of cataracts or glaucoma, nor was a dose–response relationship observed.

ICS: inhaled corticosteroid; aRR: adjusted risk ratio; RR: risk ratio; aOR: adjusted odds ratio; SABD: short-acting bronchodilator; OR: odds ratio; FSC: fluticasone propionate/salmeterol fixed-dose combination; LABA: long-acting β_2-agonist; TB: tuberculosis: NTM: nontuberculous mycobacteria; NTM-PD: nontuberculous mycobacteria pulmonary disease; OCS: oral corticosteroid.

increased the risk of new-onset diabetes (HR 1.06, 95% CI 1.00–1.13, p=0.06; I^2=79%) [49, 54, 62, 64] (figure 4). This analysis included the most conservative estimate (risk associated with low-dose ICS) of one study [64], that showed a dose–response relationship with the HR ranging from 1.076–1.150 from low- to high-dose ICSs (all p<0.0001).

Among the five cohort studies, two found an association between ICSs and risk of diabetes onset [44, 63], one found an increased risk to progression to insulin treatment with high ICS doses [62] and another found an association between high ICS doses and increased risk of diabetes-related hospitalisations [45]. Only one study did not find an association between ICS use and diabetes [49] (table 1). Two NCCs also found a positive association between exposure to ICSs and an increased risk in diabetes-related outcomes, in particular with high doses of ICSs [83, 98] (table 2).

Local complications
Eye disorders
13 studies reported this outcome (nine RCTs, two cohort studies and three NCC studies). The pooled analysis of nine RCTs with 40 981 participants showed that exposure to ICSs was associated with a trend to a higher risk of an eye disorder, but the increase was not statistically significant (RR 1.08, 95% CI 0.93–1.25; p=0.32; I^2=0%) [9, 14, 16, 18, 24, 25, 29, 34, 40] (supplementary figure S4). The results did not change when evaluating cataracts or other eye disorders separately (supplementary figure S5).

Two additional cohort studies assessed this outcome, with conflicting results. While one study [49] observed an increased risk of cataract development associated with cumulative ICS exposure (HR 1.43,
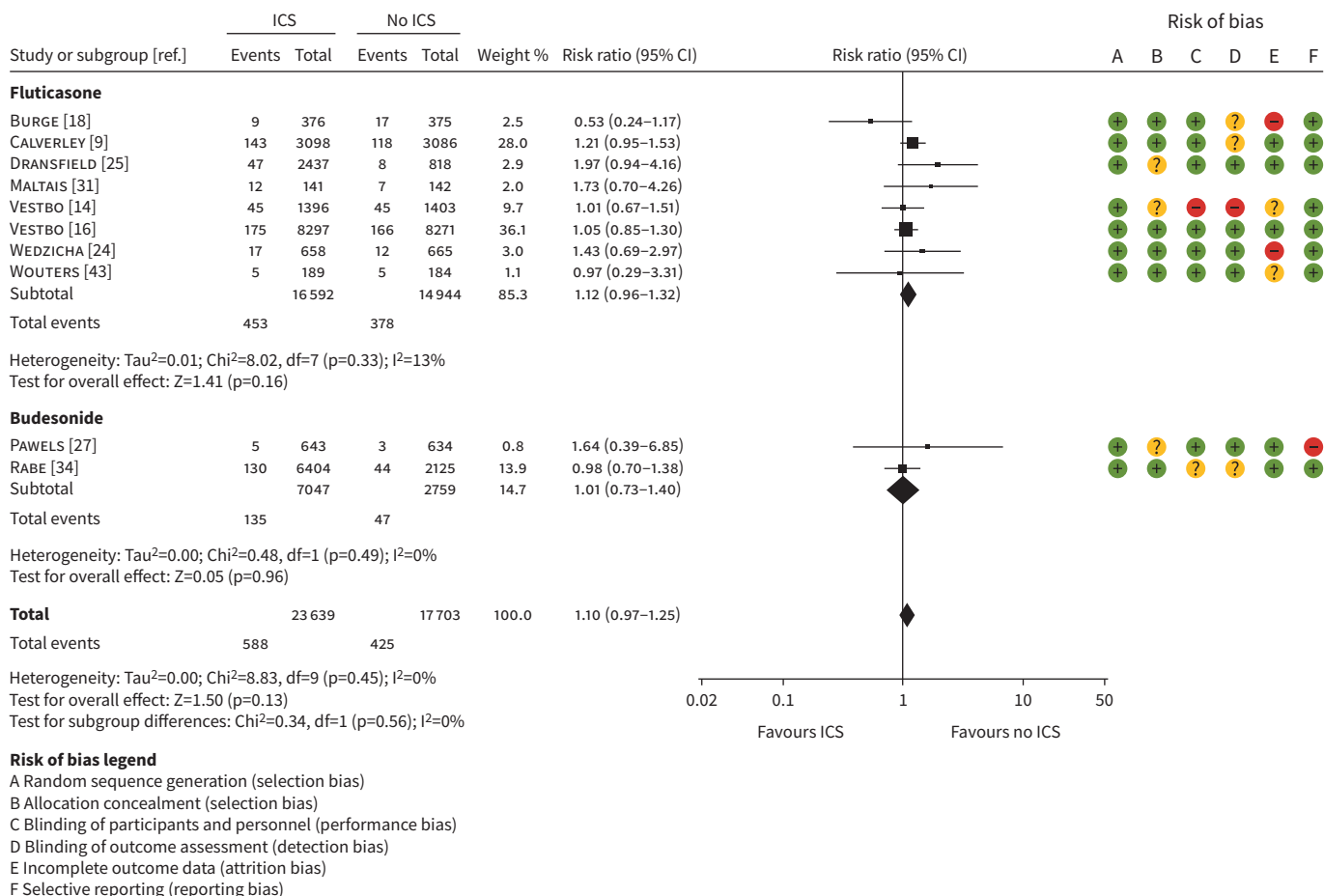
Study or subgroup [ref.]	ICS Events	Total	No ICS Events	Total	Weight %	Risk ratio (95% CI)	Risk ratio (95% CI)	Risk of bias A B C D E F
Fluticasone								
Burge [18]	9	376	17	375	2.5	0.53 (0.24–1.17)		+ + + ? − +
Calverley [9]	143	3098	118	3086	28.0	1.21 (0.95–1.53)		+ + + ? + +
Dransfield [25]	47	2437	8	818	2.9	1.97 (0.94–4.16)		+ ? + + + +
Maltais [31]	12	141	7	142	2.0	1.73 (0.70–4.26)		
Vestbo [14]	45	1396	45	1403	9.7	1.01 (0.67–1.51)		+ ? − − ? +
Vestbo [16]	175	8297	166	8271	36.1	1.05 (0.85–1.30)		+ + + + + +
Wedzicha [24]	17	658	12	665	3.0	1.43 (0.69–2.97)		+ + + + − +
Wouters [43]	5	189	5	184	1.1	0.97 (0.29–3.31)		+ + + + ? +
Subtotal		16 592		14 944	85.3	1.12 (0.96–1.32)		
Total events	453		378					

Heterogeneity: Tau^2=0.01; Chi^2=8.02, df=7 (p=0.33); I^2=13%
Test for overall effect: Z=1.41 (p=0.16)

Budesonide								
Pawels [27]	5	643	3	634	0.8	1.64 (0.39–6.85)		+ ? + + + −
Rabe [34]	130	6404	44	2125	13.9	0.98 (0.70–1.38)		+ + ? ? + +
Subtotal		7047		2759	14.7	1.01 (0.73–1.40)		
Total events	135		47					

Heterogeneity: Tau^2=0.00; Chi^2=0.48, df=1 (p=0.49); I^2=0%
Test for overall effect: Z=0.05 (p=0.96)

Total		23 639		17 703	100.0	1.10 (0.97–1.25)		
Total events	588		425					

Heterogeneity: Tau^2=0.00; Chi^2=8.83, df=9 (p=0.45); I^2=0%
Test for overall effect: Z=1.50 (p=0.13)
Test for subgroup differences: Chi^2=0.34, df=1 (p=0.56); I^2=0%

0.02   0.1   1   10   50
Favours ICS   Favours no ICS

Risk of bias legend
A Random sequence generation (selection bias)
B Allocation concealment (selection bias)
C Blinding of participants and personnel (performance bias)
D Blinding of outcome assessment (detection bias)
E Incomplete outcome data (attrition bias)
F Selective reporting (reporting bias)

FIGURE 2 Pooled risk ratios for fractures (Mantel-Haenszel, random-effects model). ICS: inhaled corticosteroid.

95% CI 1.11–1.84), another study [54] reporting on patients undergoing cataract surgery did not observe this association (HR 0.93, 95% CI 0.88–0.98). Only one of the three NCC studies found a significant association between ICS use and cataract development [86], but no association with glaucoma was described [85, 93, 96] (table 2).
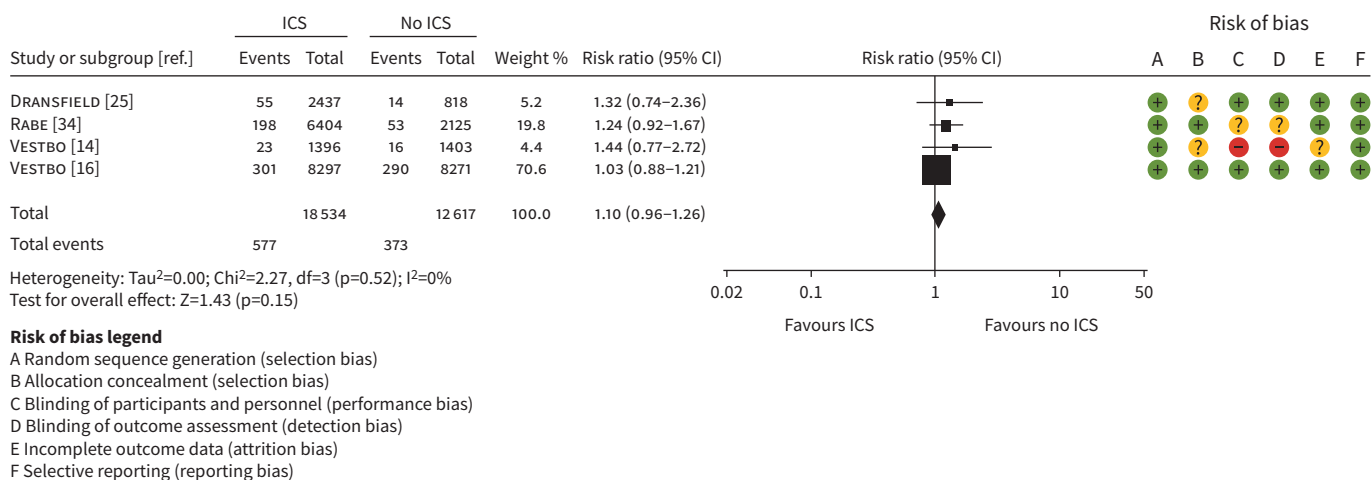
Study or subgroup [ref.]	ICS Events	Total	No ICS Events	Total	Weight %	Risk ratio (95% CI)	Risk ratio (95% CI)	Risk of bias A B C D E F
Dransfield [25]	55	2437	14	818	5.2	1.32 (0.74–2.36)		+ ? + + + +
Rabe [34]	198	6404	53	2125	19.8	1.24 (0.92–1.67)		+ + ? ? + +
Vestbo [14]	23	1396	16	1403	4.4	1.44 (0.77–2.72)		+ ? − − ? +
Vestbo [16]	301	8297	290	8271	70.6	1.03 (0.88–1.21)		+ + + + + +
Total		18 534		12 617	100.0	1.10 (0.96–1.26)		
Total events	577		373					

Heterogeneity: Tau^2=0.00; Chi^2=2.27, df=3 (p=0.52); I^2=0%
Test for overall effect: Z=1.43 (p=0.15)

0.02   0.1   1   10   50
Favours ICS   Favours no ICS

Risk of bias legend
A Random sequence generation (selection bias)
B Allocation concealment (selection bias)
C Blinding of participants and personnel (performance bias)
D Blinding of outcome assessment (detection bias)
E Incomplete outcome data (attrition bias)
F Selective reporting (reporting bias)

FIGURE 3 Pooled risk ratios for diabetes (Mantel-Haenszel, random-effects model) in randomised clinical trials. Vestbo [14] and Dransfield [25] measured effects on glucose levels; Vestbo [16] and Rabe [34] measured hyperglycaemia/new-onset diabetes mellitus. ICS: inhaled corticosteroid.
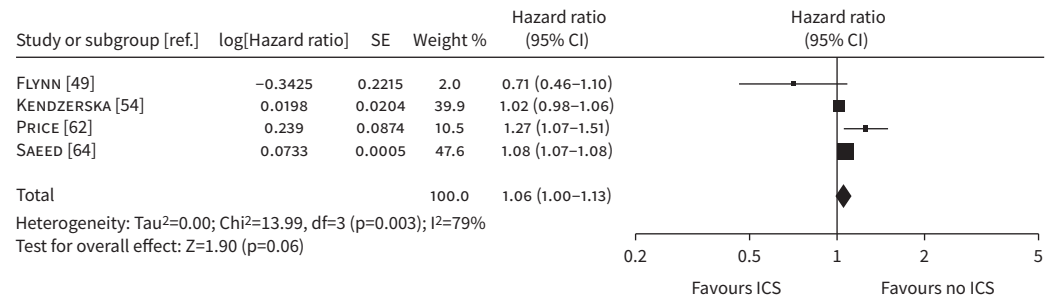
Study or subgroup [ref.]	log[Hazard ratio]	SE	Weight %	Hazard ratio (95% CI)
Flynn [49]	−0.3425	0.2215	2.0	0.71 (0.46–1.10)
Kendzerska [54]	0.0198	0.0204	39.9	1.02 (0.98–1.06)
Price [62]	0.239	0.0874	10.5	1.27 (1.07–1.51)
Saeed [64]	0.0733	0.0005	47.6	1.08 (1.07–1.08)
Total			100.0	1.06 (1.00–1.13)

Heterogeneity: Tau^2=0.00; Chi^2=13.99, df=3 (p=0.003); I^2=79%
Test for overall effect: Z=1.90 (p=0.06)

FIGURE 4 Pooled hazard ratios for diabetes (inverse variance method, random-effects model) in cohort studies. Data from Saeed [64] refer exclusively to patients treated with low-dose inhaled corticosteroids (ICS).

Oral candidiasis

The pooled analysis of 16 RCTs with 33 725 participants showed that exposure to ICSs almost tripled the risk of oral candidiasis (RR 2.89, 95% CI 2.36–3.55; p<0.00001; I^2=32%) [9, 12, 18–20, 22, 24, 26, 27, 33–35, 38–40, 43] (supplementary figure S6). The results were quite consistent across studies and also according to the ICS used.

Only one cohort study assessed this outcome [48]. The rate of oral candidiasis in patients exposed to ICSs was 5.5%, with a significant increased risk compared with non-ICS users. No significant difference was observed between patients exposed to budesonide and fluticasone. A pattern of increasing odds for oral candidiasis with increasing ICS dose was observed [48].

Dysphonia

The pooled analysis of nine RCTs with 22 841 participants showed that exposure to ICSs increased the risk of dysphonia by 277% (RR 3.77, 95% CI 2.81–5.05; p<0.00001; I^2=0%) [9, 12, 13, 18, 22, 29, 34, 35, 38] (supplementary figure S7). The results were highly consistent across studies and also according to the ICS used.

Other adverse events
Hypertension

The pooled analysis of eight RCTs with 48 207 participants showed that exposure to ICSs was not significantly associated with an increased risk of hypertension overall (RR 1.05, 95% CI 0.89–1.24; p=0.57; I^2=39%) [9, 14, 17, 22, 30, 33, 34, 36] (supplementary figure S8).

Adrenal suppression

Two RCTs assessed this outcome. One case of adrenal insufficiency in patients assigned to fluticasone (n=4135) was observed in one study [16]. The other trial found no evidence that long-term use of a moderate dose of inhaled triamcinolone suppresses either basal or stimulated adrenal function in older patients with COPD (n=221) [41].

Discussion

Treatment of respiratory diseases with ICSs has significantly reduced the risk of side-effects associated with the chronic use of oral corticosteroids; however, the use of ICSs is not free from possible complications. In this systematic review we observed a significantly increased risk of local side-effects, such as oral candidiasis and dysphonia; and an increased risk of some systemic effects such as respiratory infections (pneumonia and mycobacterial disease). Other systemic side-effects such as diabetes-related outcomes and bone fractures were only significantly associated with ICSs at high doses and with prolonged exposures in some studies, especially cohort and NCC studies. Finally, we could not find clear evidence of increased risk of sepsis, eye disorders, hypertension or adrenal suppression.

In this analysis we included not only RCTs, but also cohort and NCC studies, because most RCTs have a duration of 1 year, and this duration may not be long enough to investigate the risk associated with ICSs treatment. It should be taken into account that patients with COPD could be treated with ICSs for decades, and these patients are usually elderly with frequent comorbidities [8], making them more susceptible to the development of corticosteroid-related side-effects. The quality of the RCTs included in the meta-analyses was, in general, high. Only observational studies were included in the narrative review (with the exception

of a few cohort studies) and these studies were not used to estimate the magnitude of the associations between ICSs and side-effects; therefore, no quality analysis was conducted. In general, the quality of observational studies is low (or at best moderate) because: 1) control of confounding variables is not adequate; 2) there is no blinding of the interventions to prevent measurement errors; and 3) they are often retrospective and collect information from registries of medical records from administrative databases. For these reasons, they have only been included in our review as complementary information. The descriptive data in supplementary table S2 provide complete details about the characteristics of these studies that will help the interested reader to interpret their results.

An increased susceptibility to infections is a recognised side-effect of the use of systemic corticosteroids. Among other properties, corticosteroids, including ICS, decrease the macrophage production of cytokines that is required for antibacterial immunity [101]. Our meta-analysis of data from 19 RCTs demonstrated a 41% increased risk of pneumonia with ICS, and this significant increase was also observed in cohort and NCC studies. The increased risk of pneumonia was well identified in the 3-year TORCH study with fluticasone propionate [9]. Since then, several studies and reviews have confirmed this association. In 2014, a Cochrane review concluded that the use of ICSs in COPD was associated with an increased risk of serious adverse pneumonia events, but it did not significantly affect mortality [102]. The authors could not find significant differences in risk between fluticasone propionate and budesonide. In contrast, we observed a reduced risk of pneumonia with budesonide compared with fluticasone, as suggested by other authors [52]. A recent systematic review of evidence from direct-comparison studies showed a significantly increased risk of 13.5% and 14.4% for pneumonia and severe pneumonia, respectively, among fluticasone compared with budesonide users [103].

The risk associated with the use of ICSs may be more relevant in patients with other risk factors for pneumonia. In two replicate, 1-year studies, the risk factors associated with at least a two-fold increase in the risk of pneumonia with fluticasone furoate treatment were being a current smoker, having prior pneumonia, a body mass index <25 kg·m^{-2}, and severe airflow limitation [104]. Another factor to consider is the blood eosinophil count, since an increased risk of pneumonia has been observed when ICSs are prescribed to COPD patients with low blood eosinophil counts [105], and particularly if they have chronic bronchial infection or associated bronchiectasis [106].

The immunosuppressive effect of ICSs has been related to an increased risk of TB and nontuberculous mycobacteria pulmonary disease (NTM-PD); however, this effect has not been observed in RCTs due to the low incidence of cases of mycobacterial disease. A recent study observed an incidence rate of TB ranging from 0.15 to 0.17 per 100 person-years in fluticasone or budesonide users, respectively [75], which is approximately 100 times lower than the incidence of pneumonia in ICS users with COPD [52, 72]. Therefore, the impact of ICSs on pulmonary mycobacterial diseases should be explored in large observational studies. The majority of cohort and NCC studies indicated a significant increase in the risk of TB and NTM-PD associated with the use of higher ICS doses, without a clear difference between fluticasone and budesonide [56, 65, 75–78, 90, 92]. Interestingly, one of the most important risk factors for the development of TB in ICS users is a previous history of TB [56, 92]; therefore, the incidence of TB in patients with COPD treated with ICSs is very different in different geographic areas depending on the prevalence of TB in the area. Another interesting observation is that the use of oral corticosteroids is more strongly associated with the development of TB, and consequently, the increase in risk of TB associated with the use of ICSs is not observed in patients using oral corticosteroids simultaneously [76, 78].

The number of studies dedicated to the risk of NTM-PD is very limited, but they consistently show an increased risk with the use of ICS. ANDRÉJAK et al. [77] observed a significantly increased risk of NTM-PD in patients with COPD compared with controls, which was significantly higher with the current use of ICS, with higher doses of ICSs and with an increased number of previous hospital admissions. The adjusted OR for NTM-PD for COPD patients with current ICS use versus controls was 29.1 (95% CI 13.3–63.8).

In a large RCT, the use of triamcinolone was associated with a significant reduction of BMD [42], which was not observed in shorter, 1-year RCTs. Additionally, cohort studies show a relationship of ICS use with significant BMD decline and a dose–response relationship, with a significant effect at ICS doses of 500 µg·day^{-1} or greater [46, 51]. It is unclear whether and how these effects translate to fractures. The NCC studies showed a similar effect of ICSs in terms of an increase in risk of fractures with a dose–response relationship and only significant at high doses [84, 87, 89, 93, 95]. However, results from RCTs and cohort studies did not show a significant risk of fractures associated with ICS use. The lack of association observed in RCTs may be due to the shorter duration of observation and the selection of

participants of a younger age and with fewer comorbidities. From the evaluation of the results, it appears that the risk of fractures is only significant when ICSs are used at high doses during prolonged periods of time and in particular in patients with other risk factors. One of the largest studies [84] found a 10% increased risk of fractures with the use of fluticasone at doses ⩾1000 µg·day^{-1} for >4 years and an 11% increased risk with budesonide at doses ⩾1600 µg·day^{-1} for >4 years. However, there are some uncertainties about this modest but significant increase in the risk of fractures. In fact, in a recent narrative review of the evidence, CARAMORI et al. [107] concluded that the exact relationship between long-term ICS use and bone fracture incidence in patients with COPD remains unclear, primarily due to the lack of information about baseline BMD and other risk factors for fractures such as smoking or physical activity as well as a lack of a standardised definition of fractures.

Systemic corticosteroids are known to increase the risk of diabetes, but the risk associated with ICSs is less clear. This is particularly important, because in most studies diabetes appears as one of the most frequent comorbidities in patients with COPD [8]. The meta-analysis of RCTs did not show a significant effect of ICSs on the risk of diabetes; however, the cohort and the NCC studies consistently showed an increased risk of diabetes-related outcomes, in particular when high doses of ICSs are used. A large study in Canada showed a 34% increase in the rate of diabetes and another 34% increase in the risk of diabetes progression, with these risks increasing to 64% and 54%, respectively, with the use of high doses of fluticasone of ⩾1000 µg·day^{-1} [98].

We could not conclusively demonstrate an increased risk of eye disorders associated with ICS use in COPD. The pooled analysis of data from eight RCTs did not show a significant effect of ICSs on different eye problems. No evidence of an increased risk of glaucoma was observed in the cohort and NCC studies either; however, results for the associated risk of cataracts were more conflicting. One cohort and one NCC study found a significantly increased risk of cataracts associated with the cumulative ICS exposure [49, 85], while two other studies did not find any significant associations [54, 93].

In contrast to eye disorders, the results observed with other local side-effects such as oral candidiasis and dysphonia were much clearer. The use of ICSs was associated with an almost three-fold higher risk of oral candidiasis and almost 3.5-fold higher risk of dysphonia compared with non-users, without significant differences between different drugs. The high frequency of these disorders has been well documented in RCTs and also in observational studies and, although not severe, may result in discontinuation of treatment in some cases.

Since the long-term use of systemic corticosteroids may increase the risk of hypertension and adrenal suppression, we also wanted to investigate the evidence of a possible increase in the risk of these complications with the use of ICS. The pooled analysis of eight RCTs did not observe an increased risk of hypertension, and one RCT found only one case of adrenal insufficiency among >4000 patients treated with fluticasone [16]; consequently, no reliable conclusions could be drawn about the risk of adrenal suppression associated with the use of ICS.

Our study has attempted to provide a comprehensive overview of the risks associated with the use of ICSs in patients with COPD. However, it has the limitation that our search was restricted to studies on patients with COPD, and therefore, we may have missed some information from studies that analysed the adverse effects of ICSs in respiratory patients in general, without a clear identification of those with COPD.

In conclusion, we observed that the use of ICSs in patients with COPD is associated with an increased risk of several side-effects. The highest risk corresponded to local disorders, such as oral candidiasis and dysphonia, followed by infectious complications such as pneumonia and mycobacterial diseases, and diabetes-related outcomes, although with lower frequency. The risks of osteoporosis, bone fractures and eye disorders are less clear. For most of these complications a dose–response relationship was observed, indicating that lower doses of ICS should be used in patients with COPD whenever possible. This information should help clinicians to make informed decisions about the prescription of ICSs in patients with COPD.

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