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REVIEW ARTICLE

Intraclass comparison of inhaled corticosteroids for the risk of pneumonia in chronic obstructive pulmonary airway disorder: a network meta-analysis and meta-regression

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Abstract

Background Inhalational corticosteroids (ICS) were observed to increase the pneumonia risk in chronic obstructive pulmonary airway disorder (COPD). However, it is unknown whether any differences exist between the drugs within the ICS class.

Aim This study aimed to evaluate the risk of pneumonia associated with different ICS and identify factors that predict pneumonia in patients with moderate-to-severe COPD using a network meta-analysis.

Method Electronic databases (Medline, Cochrane CENTRAL and Google Scholar) were searched for trials comparing ICS in COPD patients. The outcomes were pneumonia and serious pneumonia. Odds ratios (OR) with 95% confidence interval (95% CI) were estimated. Meta-regression was used to identify the predictors. The strength of evidence was graded using the Grading of Recommendations, Assessment, Development, and Evaluations approach.

Results Sixty-six studies (103,347 participants) were included. Fluticasone (OR: 1.46; 95% CI: 1.26, 1.7), mometasone (OR: 2.2; 95% CI: 1.05, 4.6), and beclometasone (OR: 1.7; 95% CI: 1.1, 2.6) were observed with an increased pneumonia risk compared to placebo. Fluticasone (OR: 1.5; 95% CI: 1.3, 1.7) was observed with an increased risk of serious pneumonia. High doses (OR: 1.2; 95% CI: 1.03, 1.4), BMI $\geq$ 25 kg/m^2 (OR: 1.6; 95% CI: 1.1, 2.2), and history of exacerbations in the preceding year predicted the pneumonia risk. Evidence strength was moderate.

Conclusion ICS class differences in pneumonia risk were observed in terms of pooled effect estimates but it is unlikely that any clinically relevant differences exist. Risk–benefit analysis supports ICS use in moderate-severe COPD.

Keywords Beclometasone · Budesonide · Fluticasone · Mometasone

Impact statements

- Clinicians should consider dosage, body mass index, and exacerbation history while prescribing inhalational corticosteroids to mitigate the risk of pneumonia.
- Pharmacists should educate patients about the risk of pneumonia while dispensing inhalational corticosteroids.
- Protocols should be implemented in the healthcare delivery system emphasizing the need for regular assessment of patients on inhalational corticosteroids on the pneumonia risk.

Introduction

Chronic obstructive pulmonary airway disorder (COPD) is one of the leading causes of mortality, primarily due to acute exacerbations [1]. Inhaled corticosteroids (ICS) are one of the effective drug classes to curtail acute exacerbations in COPD, especially in moderate to very severe stages [2]. Nearly 50–80% of such patients were estimated to use ICS of which approximately 25% demonstrate a reduction in the incidence and severity of acute exacerbation in COPD [3, 4]. As per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 recommendations, ICS therapy is indicated in patients with history of moderate exacerbations in the preceding year,

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hospitalization for COPD exacerbations, blood eosinophil count > 300/µl or those with concurrent asthma [5]. ICS therapy is preferably not to be administered alone as they have not been shown to modify either the decline in lung function or mortality on long term use [6]. Further, ICS alone has shown an increased risk of mortality compared to the combination with long-acting beta-2 agonist [7]. Depending on the definitions of the endpoint related to reduction in the incidence of COPD exacerbation, the number needed to treat (NNT) for ICS has been observed to range between 3 and 7 [8].

Long-term use of ICS was observed to result in altered glycemic control, osteoporosis, cataract, and oropharyngeal side effects [9]. Several studies have observed a strong association between ICS use and pneumonia with advanced age, male gender, low body mass index, and decreased airflow were identified as risk factors [10]. Several direct comparison meta-analyses were carried out evaluating the risk of pneumonia with ICS therapies and had contradictory conclusions [11–13]. A recent direct comparison meta-analysis included 59 randomized clinical trials but was observed with a lot of drawbacks such as the inclusion of erroneous data, publication bias was not assessed, and grading of the evidence was not carried out [14]. Lodise et al. [15] examined the variations within a single class of drugs, specifically fluticasone and budesonide, concerning the risk of pneumonia in individuals with chronic obstructive pulmonary disease (COPD). However, this study had some limitations. Firstly, it only collected data from five studies that directly compared fluticasone and budesonide. Additionally, out of these five studies, only one was a randomized trial, while the others were observational studies. Furthermore, the authors mistakenly combined data from both study designs to generate overall estimates, which was not appropriate. Hence, it is unclear whether any difference exists in terms of pneumonia risk within the ICS class of drugs, between fluticasone, budesonide, mometasone, and beclometasone. This is mainly limited by the presence of very few studies comparing the occurrence of pneumonia in clinical trials using head-to-head ICS therapies. Unfortunately, such head-to-head comparison trials in the absence of non-ICS comparators could not be included in the previous meta-analysis due to the limitations of the traditional direct comparison meta-analysis. A network meta-analysis (NMA) provides pooled estimates using direct and indirect comparisons through a common comparator [16]. Through NMA, effect estimates can be generated between the interventions even in the absence (or limited number) of head-to-head comparison clinical trials. Moreover, previous meta-analyses have failed to identify any risk factors associated with pneumonia risk that can only be evaluated using meta-regression techniques.

Aim

This study aimed to evaluate the risk of pneumonia associated with different ICS and identify factors that predict pneumonia in patients with moderate-to-severe COPD using a network meta-analysis.

Method

Search strategy

The protocol for this systematic review is accessible in the Open Science Framework [17]. Medline, Cochrane CENTRAL and Google Scholar were the databases searched for articles. The search strategy is provided in the Electronic Supplementary Table 1. Only randomized clinical trials meeting the PICO criteria published until 2nd November 2023 were included. No limits were placed either with the publication year or language. We also carried out a hand search of the published articles to find suitable publications.

Eligibility criteria

We included studies that met the following eligibility criteria:

Population: Adults of either gender diagnosed with COPD.
Intervention: ICS of any dose and through any device.
Control: Placebo/No ICS/ICS of any dose and through any device.
Outcome: The Medical Dictionary for Regulatory Activities (MedDRA) defined pneumonia as mentioned by the preferred terms such as pneumonia, lobar pneumonia, and bronchopneumonia as the primary outcome. Additionally, we also considered serious pneumonia as defined by the authors either as a serious adverse event or pneumonia leading to death as a secondary outcome.

Study procedure

Two authors independently searched for eligible studies and obtained the following details from each eligible study: Trial identification, site, year, participants, interventions, and outcomes. Any disagreement was resolved through discussion and a consensus was reached. The present network meta-analysis complies with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) [18]. Cochrane risk of bias tool was used for assessing the risk of bias of the included studies on the following domains:

generation of random sequence; concealment of allocation; blinding of participants, study personnel, and outcome assessment; incomplete outcome reporting; and selective reporting of outcomes [19]. For comparisons with at least five studies, we assessed the publication bias using the Funnel plot and Begg and Mazumdar test [20]. We used a random-effects model for obtaining the direct, indirect, and mixed treatment comparison pooled estimates. The direct comparison pooled estimates were obtained from the data included in the head-to-head clinical trials while the indirect pooled estimates were obtained from the trials using common comparators. Mixed treatment comparison estimates were obtained from the data from studies included for both direct and indirect comparison pooled estimates. The effect estimates were represented using odds ratios [95% confidence intervals] (OR, 95% CI). We used H statistics for evaluating the inconsistency between direct and indirect pooled estimates, and the inconsistency was classified as follows: mild (< 3), modest (3–6), and large (> 6) [21]. A separate analysis was carried out to obtain the pooled estimates between various doses of ICS. The doses were classified into low, medium, and high doses according to the National Institute for Health and Care Excellence (NICE) recommendations (Electronic Supplementary Table 2). Sensitivity analysis was carried out by excluding the estimates from studies with the potential high risk of bias. Leave-one-out meta-analysis was carried out by excluding the data of one study at a time and observing its impact on the pooled estimates. Cumulative meta-analysis was carried out where the studies were added chronologically and the changes in the pooled estimates obtained before the addition were analyzed. We used MetaXL© to estimate the mixed comparison pooled estimates [22]. The final estimates were graded using the grades of recommendation, assessment, development, and evaluation (GRADE) working group approach [23]. VOSviewer© was used for constructing and analyzing the bibliometric networks for identifying common author groups involved in the included trials [24]. Litmap© was used for mapping the included articles where the most recent articles are placed on the right-most column and the most cited articles on the top and the connecting lines between them indicate the citations between the included articles [25]. Meta-regression for the pneumonia risk was carried out with the following variables as covariates: ICS intervention (fluticasone, budesonide, mometasone, and beclometasone), doses (low, medium, and high), age (< 65, and ≥ 65 years), body mass index (BMI) (< 25 and ≥ 25 kg/m^2), concomitant drug classes (LABA, LAMA, LABA plus LAMA, and ICS alone), pack-years of smoking (< 10 and ≥ 10), GOLD stage (I, II, and III/IV), number of previous exacerbations (0, 1, and ≥ 2), blood eosinophilia (< 300 and ≥ 300cells/mm^3), and duration of ICS treatment (< 24and ≥ 24 weeks). A few studies did not report BMI and imputed with the median values. Meta-regression was carried out using the maximum likelihood random-effects method and the output on the natural logarithm of odds (Ln[odds]) was converted to OR. We attempted to estimate the number needed to harm (NNH) with 95% CI were estimated based on the pooled risk differences across the studies. Meta-regression, leave-on-out, and cumulative meta-analysis were carried out by OpenMEE [26]. A p-value of ≤ 0.05 was considered significant for covariates obtained in meta-regression and for RR and NNH values. We carried out a Trial sequential analysis (TSA, Copenhagen, DK) for comparisons with significant pooled estimates against the control group for assessing the power of evidence that has accumulated so far in obtaining the pooled estimates [27].

Results

Search results

One thousand six hundred and forty-one articles were obtained with the search strategy. The PRISMA flowchart of the articles from screening until the final inclusion is depicted in Fig. 1. Sixty-six studies (103,387 participants) [28–93] were included in this systematic review. Key characteristics of the included studies in the review are mentioned in the Electronic Supplementary Table 3. Litmap© revealed that Burge et al. [35], Wedzicha et al. [87], and Aaron et al. [28] were the most cited (Electronic Supplementary Figure 1). Bibliometric analyses revealed two clusters of authors commonly involved in publishing research articles in this area (Electronic Supplementary Figure 2). Two studies [41, 69] were included in the systematic review but were excluded from the meta-analysis as they provided the estimates for the outcome in terms of rate and not in proportion. These studies compared high and medium doses of fluticasone plus salmeterol, and fluticasone plus umeclidinium plus vilanterol, respectively. Another study [48] compared medium with high doses of fluticasone plus salmeterol and was included only in the sub-group analysis. A summary of the risk of bias in included studies is depicted in the Electronic Supplementary Figure 3. Most studies had low risk while a few studies had a high risk of bias in the selection, performance, and detection bias. Details of the risk of bias for individual studies are depicted in the Electronic Supplementary Figure 4.

Pooled estimates for the pneumonia risk

Sixty-one studies (100,934 patients) reported this outcome and were included in this analysis. The network plot depicting the relationship between the interventions assessed for this outcome is depicted in Fig. 2. The comparison between

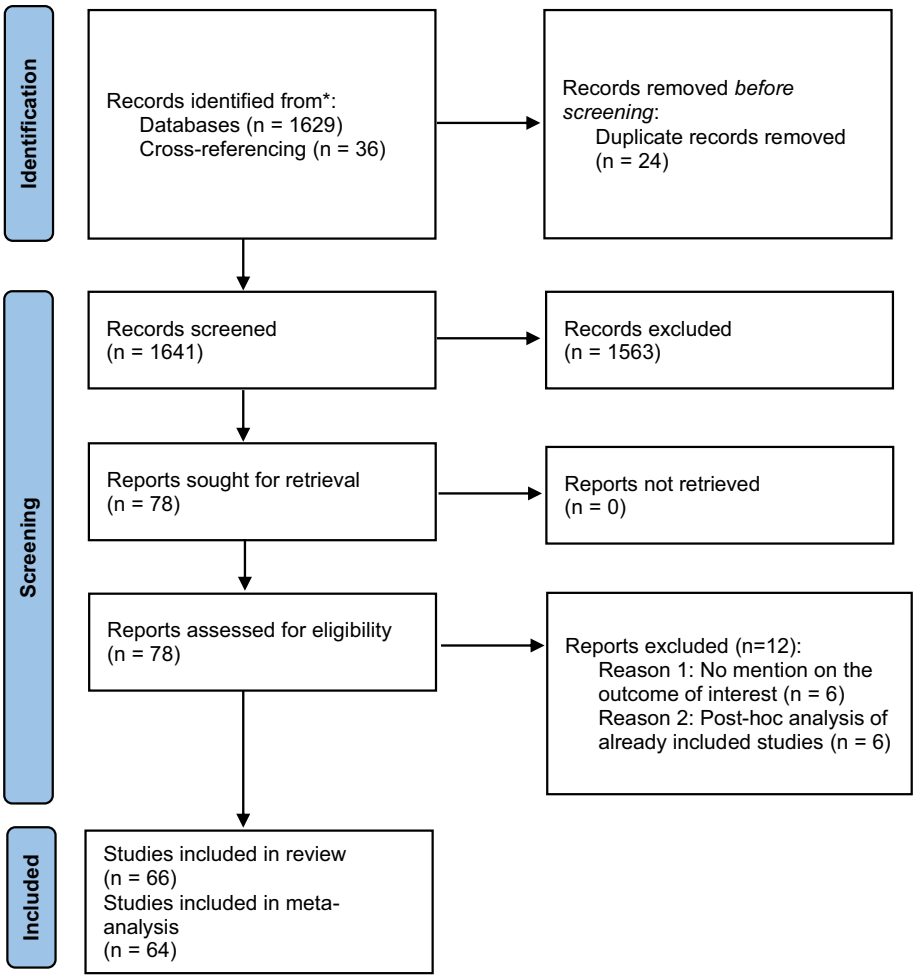

Fig. 1 PRISMA flow diagram. One thousand six hundred and forty-one articles were obtained with the search strategy out of which 66 were included in this systematic review and 64 in this meta-analysis

budesonide/formoterol/indacaterol/tiotropium with indacaterol/tiotropium could not be analyzed as there was no common comparator with either of these medical therapies. The mixed treatment comparison estimates for each of the interventions in comparison with placebo are depicted in Fig. 3. Fluticasone (OR: 1.46; 95% CI: 1.26, 1.7), fluticasone plus salmeterol (OR: 1.74; 95% CI: 1.38, 2.19), and mometasone plus formoterol (OR: 2.2; 95% CI: 1.05, 4.6) were observed with a high risk of pneumonia compared to placebo. Mild inconsistency was observed (H value of 1.041).

When the individual ICS was compared against all the control interventions, fluticasone (OR: 1.5; 95% CI: 1.3, 1.7) and beclometasone (OR: 1.7; 95% CI: 1.1, 2.6) showed a significantly increased risk of pneumonia while no significant differences were observed among the other ICS (Electronic Supplementary Figure 5). Mild inconsistency was observed (H value of 1).

Pooled estimates for the risk of serious pneumonia

Twenty-four studies (42,847 patients) were included in the analysis of this outcome. The network plot depicting the relationship between the interventions assessed for this outcome is depicted in the Electronic Supplementary Figure 6. None of the interventions were observed with any significant risk of serious pneumonia (Electronic Supplementary Figure 7). Mild inconsistency was observed (H value of 1).

When the individual ICS was compared against all the control interventions, only fluticasone (OR: 1.5; 95% CI: 1.3, 1.7) showed a significantly higher risk of serious pneumonia and no significant differences were observed among the ICS for the pneumonia risk (Electronic Supplementary Figure 8). Mild inconsistency was observed (H value of 1).

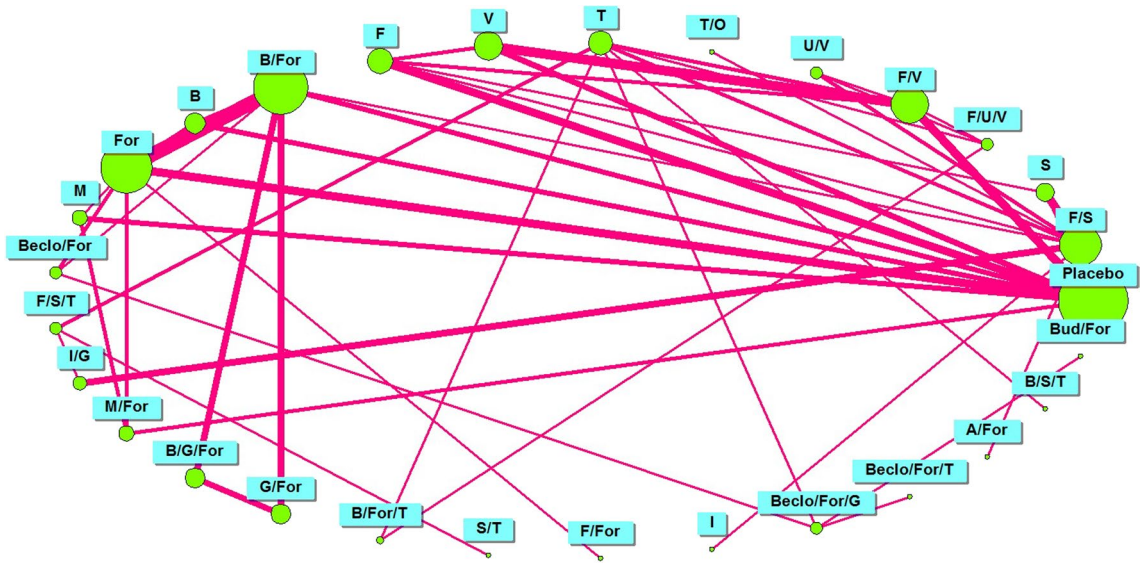

Fig. 2 Network plot of ICS interventions for the risk of pneumonia. Beclo—Beclometasone; B—Budesonide; F—Fluticasone; For—Formoterol; G—Glycopyrrolate; I—Indacaterol; M—Mometasone; O—Olodaterol; S—Salmeterol; T—Tiotropium; U—Umeclidinium; and V—Vilanterol. Nine studies compared inhalational budesonide plus formoterol with formoterol, six compared fluticasone plus vilanterol with vilanterol, and five each compared fluticasone plus salmeterol with salmeterol, fluticasone plus vilanterol with placebo, and formoterol with placebo, followed by others

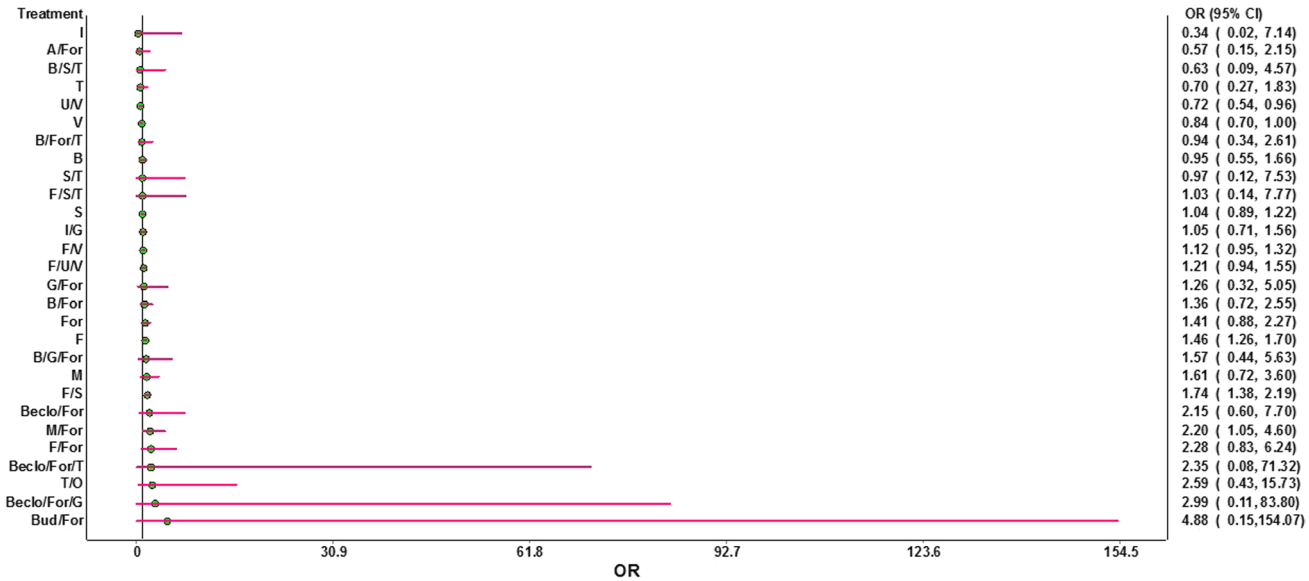

Fig. 3 Forest plot of the individual ICS for the risk of pneumonia compared to placebo. Beclo—Beclomethasone; B—Budesonide; F—Fluticasone; For—Formoterol; G—Glycopyrrolate; I—Indacaterol; M—Mometasone; O—Olodaterol; S—Salmeterol; T—Tiotropium; U—Umeclidinium; V—Vilanterol; OR—Odds ratio; and CI—Confidence interval. The X-axis indicates the odds ratio and the Y-axis on the left side indicates the various drug treatment/s and odds ratios with 95% confidence intervals are represented on the right side. The green circle indicates the point estimates, and the pink line represents the 95% confidence interval. The vertical black line indicates the line of no difference between the interventions

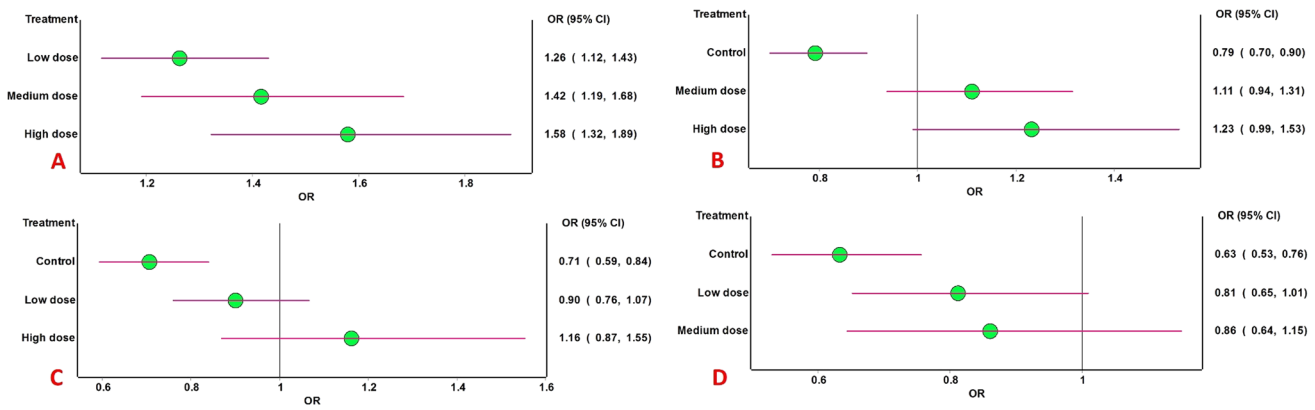

Fig. 4 Forest plot comparing the ICS doses for the risk of pneumonia. Forest plots comparing the ICS therapy for the risk of pneumonia. The comparators are A—Control; B—Low doses of ICS; C—Medium doses of ICS; and D—High doses of ICS. The X-axis indicates the odds ratio and the Y-axis on the left side indicates the various drug treatment/s and odds ratios with 95% confidence intervals are represented on the right side. The green circle indicates the point estimates and the pink line represents the 95% confidence interval. The vertical black line indicates the line of no difference between the interventions

Pooled estimates comparing the various doses of ICS

Low (OR: 1.26; 95% CI: 1.12, 1.43), medium (OR: 1.42; 95% CI: 1.19, 1.68), and high doses (OR: 1.58; 95% CI: 1.32, 1.89) of ICS were associated with significantly higher risks of pneumonia compared to control group of interventions (Fig. 4). However, no significant differences were observed between the different doses (Fig. 4) albeit a trend with an increased odds ratio from low to high doses of ICS.

Medium (OR: 1.68; 95% CI: 1.19, 2.37) doses of ICS were associated with a significantly higher risk of serious pneumonia compared to the control group of interventions (Electronic Supplementary Figure 9). Also, no significant differences were observed between the different doses (Electronic Supplementary Figure 9).

Meta-regression analysis

Meta-regression analysis revealed interventions and dose categories to be the significant predictors of outcomes (Table 1). All the included studies recruited patients with at least 10 smoking pack-years and only 1 study included the details on blood eosinophil count due to which they could not be assessed in this study. Compared to fluticasone, budesonide was observed with a significantly lower risk of pneumonia. Similarly, high doses of ICS were observed with a significantly greater risk of pneumonia like those with BMI $\geq$ 25 kg/m^2. Also, those with at least

Table 1 Meta-regression analyses identifying the risk factors of pneumonia

Co-variates		OR [95% CI]
ICS therapy: compared to fluticasone	Budesonide	0.7* [0.6, 0.9]
	Mometasone	1.3 [0.6, 2.7]
	Beclomethasone	1.1 [0.7, 1.9]
Dose: Compared to low dose of ICS	Medium dose	1.1 [0.5, 1.4]
	High dose	1.2* [1.03, 1.4]
BMI: Those with $\geq$ 25 kg/m^2 compared to those with < 25 kg/m^2		1.6* [1.1, 2.2]
Age: Those aged $\geq$ 65 years compared to < 65 years		0.9 [0.7, 1.1]
Number of exacerbations in the last 12 months: Those without any previous exacerbations	1 exacerbation	1.3* [1.1, 1.5]
	$\geq$2 exacerbation	1.4* [1.2, 1.8]
GOLD stage: Those with stage II	Stage III	0.7 [0.4, 1.4]
ICS duration: Those with < 24 weeks	$\geq$24 weeks	1.1 [0.7, 1.7]
Concomitant drug classes compared to ICS alone	LABA	1.2 [0.7, 1.9]
	LABA and LAMA	1.4 [0.8, 2.3]

*Statistically significant

one previous exacerbation in the last 12 months showed a significantly increased risk of pneumonia compared to those without.

NNH analysis

Due to the very low-risk differences observed for most comparisons, NNH could be computed only for fluticasone (NNH: 100; 95% CI: 100, 50) and high doses of ICS (NNH: 100; 95% CI: 100, 50).

Publication bias

Eleven comparisons were observed with more than five studies and the funnel plots did not reveal the presence of any publication bias (Electronic Supplementary Figure 10). Begg and Mazumdar's test did not reveal publication bias for the following comparisons for pneumonia: fluticasone versus control (p = 0.8); budesonide versus control (p = 0.6); medium dose versus control (p = 0.8); low dose versus control (p = 0.9); high dose versus control (p = 0.5); fluticasone plus vilanterol (p = 0.9); and budesonide plus formoterol (p = 0.7). Similarly, no publication bias was detected for the following comparisons for serious pneumonia: fluticasone versus control (p = 0.9); budesonide versus control (p = 0.4); low dose versus control (p = 0.9); and medium dose versus control (p = 0.7).

Sensitivity analyses

Seven studies [35, 55, 57, 61, 65, 67, 80] were observed with a high risk of bias in at least one domain. Removal of the data from these studies showed similar results as that of the overall analysis and no significant difference was observed for the risk of pneumonia with mometasone plus formoterol (Electronic Supplementary Figure 11). The leave-one-out meta-analysis also revealed no significant changes in the pooled estimates when the results of each included study were removed from the analysis (Electronic Supplementary Figure 12).

Trial sequential analysis and cumulative meta-analysis

Trial sequential analysis was carried out between fluticasone and budesonide with control. Significant pooled estimates observed between these interventions are sufficient for concluding that these interventions were associated with an increased risk of pneumonia (Electronic Supplementary Figures 13 and 14). Cumulative meta-analysis revealed that data published later than Caverley et al. 2007 did not change the pooled estimates significantly (Electronic Supplementary Figure 15).

Grading the strength of evidence

Grading the evidence for the significant estimates is outlined in Table 2. Moderate strength of evidence was observed for fluticasone with control group comparison for the

Table 2 Summary of findings table mentioning the strength of evidence for the significant pooled estimates

Comparisons with placebo	Illustrative comparative risks (per 1000) (95% confidence intervals)		Effect estimates and the quality of evidence for mixed treatment comparisons
	Assumed risk[1]	Corresponding risk	
Pneumonia with fluticasone	14	20 (18–24)	1.46 [1.26, 1.7] ⊕⊕⊕⊖; **Moderate**[2]
Pneumonia with fluticasone plus salmeterol	31	53 (42–65)	1.74 [1.38, 2.19] ⊕⊕⊖⊖; **Low**[2,3]
Pneumonia with beclometasone	18	30 (20–45)	1.7 [1.1, 2.6] ⊕⊕⊖⊖; **Low**[2,3]
Serious pneumonia with fluticasone	8	12 (10–14)	1.5 [1.3, 1.7] ⊕⊕⊖⊖; **Low**[2,3]
Pneumonia with low doses of ICS	17	21 (19–24)	1.26 [1.12, 1.43] ⊕⊕⊖⊖; **Low**[2,3]
Pneumonia with medium doses of ICS	17	24 (20–28)	1.42 [1.19, 1.68] ⊕⊕⊖⊖; **Low**[2,3]
Pneumonia with high doses of ICS	15	23 (20–28)	1.58 [1.32, 1.89] ⊕⊕⊖⊖; **Low**[2,3]

1—Assumed risk was the median control group risk across the studies; 2—Downgraded one level for including studies with high risk of bias; 3—Downgraded one level as publication bias could not be assessed/ruled out; 4—Downgraded one level for serious limitations in the precision of the estimates; **Moderate:** The authors believe that the true effect is probably close to the estimated effect; and **Low:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

pneumonia risk while either low or very low strength was observed for other comparisons.

Discussion

Statement of key findings

The present network meta-analysis evaluated the risk of pneumonia with ICS therapies in COPD patients. Fluticasone, mometasone, and beclometasone were observed with a significantly increased risk of pneumonia compared to placebo. Fluticasone was observed to increase the risk of serious pneumonia. A trend of increased risk of pneumonia was observed with an increase in the ICS doses. Meta-regression analysis revealed a high risk of pneumonia with high ICS doses, BMI $\geq$ 25 kg/m^2, at least one previous exacerbation, and with fluticasone compared to budesonide. The results did not change significantly in the sensitivity analysis and the publication bias was not detected. A moderate level of certainty was observed for most of the comparisons with statistically significant pooled estimates. TSA results confirmed the adequacy of evidence for pneumonia risk for fluticasone and budesonide. Cumulative meta-analysis revealed that the pooled estimates did not change significantly with the addition of data later than the year 2007. NNH was 100 for fluticasone and high doses of ICS for the risk of pneumonia.

Strengths and weaknesses

This is the first network meta-analysis comparing the differences in the risk of pneumonia between various ICS therapies. To this date, this is the largest meta-analysis carried out evaluating the risk of this outcome. Most of the included studies were high quality with a low risk of bias. Additionally, we have also carried out robust sensitivity analysis and meta-regression for identifying the predictors of pneumonia risk with ICS therapies. We have also evaluated the NNH to make an informed decision by the clinicians and regulatory authorities. However, the study is limited in imputing values for BMI for a few studies as well as there were no studies that recruited patients with low BMI due to which we could not analyze the effect of underweight as a covariate. Future studies should also consider blood eosinophil count for stratifying patients. We observed that only one trial used a cut-off limit of blood eosinophil count as 300 cells/µl. GOLD 2023 guidelines recommend $<$ 100 and $\geq$ 300 cells/µl as cut-off [5] and should be considered in future trials for assessing the predictive ability of this factor.

Interpretation and further research

The European Medicine Agency (EMA) reviewed the data available until 2016 and concluded the risk of pneumonia with ICS therapies [94]. However, EMA has concluded that there is no conclusive evidence of any intra-class differences and the dose of ICS with pneumonia. In the present study, we observed that budesonide had a significantly lower risk of pneumonia compared to fluticasone. A similar conclusion was made from a direct comparison meta-analysis where fluticasone users were observed with a 13.5% increase in the risk of pneumonia compared to budesonide [15]. We observed an OR of 0.7 (20% decrease) for pneumonia with budesonide compared to fluticasone with a NNH difference of 92.8. Hence, it takes 90 additional patients to observe one pneumonia with budesonide compared to fluticasone. Similarly, Yang et al. carried out a direct comparison meta-analysis with 25 RCTs with 49,982 participants and concluded a significant difference between fluticasone doses and pneumonia risk but not with budesonide therapy [9]. A nationwide observational study in Korea in a total of 47,473 patients revealed that 14% of 14,518 patients receiving fluticasone developed pneumonia as like 10.66% of 14,518 patients on budesonide users [95]. A record-linked 10-year data from Sweden revealed a number needed to harm as 22 patients treated with fluticasone developed pneumonia as against one additional patient with budesonide [96]. This difference could potentially be explained by increased lipophilicity coupled with a sustained and more potent immunosuppressive effect with fluticasone [97]. Further, the deposition of fluticasone in the lungs was observed to be five times more than budesonide, and a larger fraction was excreted in the sputum [98]. The authors of that study did not include any data regarding other ICS therapies such as mometasone and beclometasone. In the present study, we have included all the ICS therapies and budesonide was observed with the least risk of developing pneumonia. However, the NNH values of fluticasone and high ICS doses were relatively higher, so it is likely that the risk–benefit balance favors the continued use of ICS in COPD patients with moderate-to-severe exacerbations. Further, due to the very low-risk differences between other ICS therapies, it is unlikely that any clinically relevant differences might exist within the ICS class.

We observed a gradient increase in the risk of pneumonia with an increase in the ICS dose. Further, high doses of ICS were observed with a 10% additional risk of pneumonia compared to low doses in the present study. A recent study revealed that the addition of low-to-moderate doses of ICS could be observed with a net clinical benefit in patients with baseline exacerbation to an extent of 54–83% [99]. As recommended in the Global Initiative for Chronic Obstructive

Lung Disease (GOLD) 2023 guidelines, de-escalation of ICS should be considered wherever possible [5–5]. Frequent episodes of pneumonia are a contraindication for receiving ICS [100]. Despite these, the GOLD 2023 guidelines do not provide any recommendations on the preference of either budesonide over fluticasone or on the doses of ICS to be initiated and titrated. It is high time the clinical differences in the key outcomes between inhalational fluticasone and budesonide are recognized in the standard treatment guidelines and recommendations emerge regarding the dosing strategies.

Body mass index was observed to be a significant predictor in the present study. Chen et al. carried out a sub-group analysis on the population from similar studies and observed that an increase in the risk of pneumonia was observed in both the groups with BMI < 25 and with ≥ 25 kg/m^2 [14]. However, in the present study, we carried out meta-regression and observed that the latter category poses a significant risk for pneumonia. Although a greater BMI was observed with an increased risk of pneumonia, those in the overweight category were observed with a reduced risk of mortality [101]. Future trials should consider personalizing the ICS therapy based on BMI values and shed more light on this predictive factor in COPD patients.

Conclusion

ICS class differences in pneumonia risk were observed in terms of pooled effect estimates but it is unlikely that any clinically relevant differences exist. Risk–benefit analysis generally supports ICS use in moderate-severe COPD. Guidelines should consider ICS type and dose. Further studies are needed to confirm the link between BMI and pneumonia risk in COPD patients receiving ICS.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11096-024-01736-8.

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Conflicts of interest The authors have no conflicts of interest to declare.

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