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High versus Medium Dose of Inhaled Corticosteroid in Chronic Obstructive Lung Disease: A Systematic Review and Meta-Analysis

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Background: Inhaled corticosteroids (ICSs) combined with bronchodilators have been identified to improve outcomes in COPD but also to be associated with certain adverse effects.

Objective: We performed a systematic review and meta-analysis to compile and summarize data on the efficacy and safety of dosing levels (high versus medium/low) of ICS alongside ancillary bronchodilators following PRISMA guidelines.

Data Sources: Medline and Embase were systematically searched until December 2021. Randomized, clinical trials (RCTs) that met predefined inclusion criteria were included.

Data Extraction: Risk ratios (RRs) with 95% confidence intervals (CI) were extracted. Any acute exacerbation of COPD (AECOPD) risk was chosen as the primary efficacy outcome, mortality rate as the primary safety outcome, moderate/severe AECOPD risk as the secondary efficacy outcome and pneumonia risk as the secondary safety outcome. Subgroup analyses of individual ICS agents, of patients with baseline moderate/severe/very severe COPD and of patients with recent COPD exacerbation history were also performed. A random-effects model was used.

Results: We included 13 RCTs in our study. No data on low doses were included in the analysis. High dose ICS was not associated with a statistically significant difference in any AECOPD risk (RR: 0.98, 95% CI: 0.91–1.05, I^2: 41.3%), mortality rate (RR: 0.99, 95% CI: 0.75–1.32, I^2: 0.0%), moderate/severe AECOPD risk (RR: 1.01, 95% CI: 0.96–1.06, I^2: 0.0%) or pneumonia risk (RR: 1.07, 95% CI: 0.86 −1.33, I^2: 9.3%) compared to medium dose ICS. The same trend was identified with the several subgroup analyses.

Conclusion: Our study collected RCTs investigating the optimal dosing level of ICS prescribed alongside ancillary bronchodilators to patients with COPD. We identified that the high ICS dose neither reduces AECOPD risk and mortality rates nor increases pneumonia risk relative to the medium dose.

Keywords: chronic obstructive lung disease, acute COPD exacerbation, mortality, pneumonia, inhaled corticosteroids

Introduction

Chronic obstructive pulmonary disease (COPD) is a medical condition that has a significant morbidity, mortality and financial toll globally.[1,2] Since their first iteration, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines have offered a stepwise approach to pharmacologic management of COPD in its stable state via the use of different inhaled medication classes.[3] The use of an inhaled corticosteroid (ICS) is not the initial recommendation but a possible subsequent one thus building double and triple therapies.

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The use of ICS is dictated by an individualized risks and benefits calculation. On one hand, they are effective in decreasing acute exacerbations of COPD (AECOPDs).[4] AECOPDs are considered the most serious complication[5–7] and a prevalent cause of mortality for patients with COPD alongside cardiovascular causes and malignancies.[8] On the other hand, ICSs have also been associated in a dose-dependent manner with potentially significant side effects, most importantly pneumonia but also others such as bone fractures and cataract.[9,10] An effect on cardiovascular mortality has not yet been definitively established[11] and some evidence of all-cause mortality benefit associated with their use has recently become available.[12,13]

A consensus on the optimal ICS dosing regimen has not been reached. Different study groups investigated a number of different agents and an even larger number of dosing regimens. We performed a systematic review of this literature and meta-analyzed the results of randomized, clinical trials (RTCs) that provided details on efficacy outcomes (risk of any AECOPD and risk of moderate/severe AECOPD) and safety outcomes (mortality rate and risk of pneumonia development) in patients with COPD in order to investigate and quantify the effect profile of different ICS doses.

Methods

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14] The study was registered with the International Prospective Register of Systematic Reviews (Identifier: CRD42021276365). The PRIMSA Checklist corroborating our methodology is presented in our Supplementary Material.

Study Selection and Eligibility Criteria

The algorithm used for the Medline and Embase databases was:

> (Inhaled AND ((glucocorticosteroids OR glucocorticoids OR corticosteroids OR steroids) OR (fluticasone OR budesonide OR mometasone OR beclomethasone OR ciclesonide))) AND (COPD OR (chronic AND obstructive AND pulmonary AND disease) OR. (chronic AND bronchitis))

In addition and in order to identify further eligible studies, manual searches of the references list of the included studies and pertinent reviews were performed.

The processing of studies proceeded with pre-specified inclusion criteria: i) RCT, ii) study population being adults (>18 years old) suffering from COPD, iii) final form of publication available online in English, iv) study comparing a high dose of ICS to a low/medium dose of the same ICS, v) concurrent use of at least one (LABA or LAMA) ancillary medication to the ICS, vi) clear definition of AECOPD and clear definition of stratification of AECOPD, if one is used, vii) studies providing outcome results as participant counts or participant groups Risks or participant groups Risk Ratio (RR) with 95% Confidence Intervals (CI) or data that would allow the calculation of counts or RR with 95% CI.

We excluded articles for the following reasons: i) duplicate reports, ii) studies that included patients without COPD, for example asthma, iii) studies that did not include COPD exacerbation as an outcome, v) studies that only included a single dose of inhaled corticosteroid, vi) studies that compared two or more different ICSs.

The databases and references review started in January 2021 and was completed in December 2021 by two researcher teams led by PAB and TT. A third independent investigator (SF) was involved as needed to reach consensus.

Data Extraction and Outcomes

Two independent reviewers (JYY and GJHR) blinded to each other extracted data from the included studies using for all pertinent variables in a predefined data collection form. Discrepancies were resolved with the involvement of a third reviewer (PAB). Data for the following baseline variables were extracted: first author, year of publication, time period of trial interventions, nature of population enrolled, definition of AECOPD used in the study, type and dosage of ICS, type of accompanying LABA/LAMA, number of participants enrolled, age of participants, gender distribution of participants, distribution of pack-years of smoking, mean forced expiratory volume in the first second (FEV1), number of participants with COPD severity of stage 2–4 according to GOLD, number of participants with recent AECOPD.

We chose our study's outcomes focusing on clinically meaningful outcomes as well as outcomes with the lowest possible exposure to different types of bias. As such, our primary efficacy endpoint was the RR with 95% CI of any AECOPD between the ICS dose levels during the investigational period and the secondary efficacy endpoint was the RR with 95% CI of moderate/severe AECOPD. Our primary safety endpoint was the RR with 95% CI of mortality between the ICS dose levels during the investigational period and our secondary safety endpoint was the RR with 95% CI of development of pneumonia. The definition of AECOPD and pneumonia was accepted as provided by the authors of the primary study.

The ICS steroid levels were classified as per usual medical practice with the maximal dose representing the "High" dose for our investigational purposes and everything less than that representing the "Low/Medium" dose. We collected counts, risks or RRs with 95% CI both for our main data collection but also for a pre-determined number of subgroups of interest. The first analysis was performed on subgroups based on the individual ICS agent used, the second on the subgroup of patients with moderate/severe/very severe COPD at baseline (as per GOLD classification) and the third on the subgroup of patients with a recent AECOPD (within 1 year from study enrollment).

Risk of Bias Assessment

Two independent reviewers (TT, VG) assessed the risk of bias of the included studies using the Revised Cochrane risk-of -bias tool (RoB 2) for randomized studies.[15]

Data Synthesis and Statistical Analysis

The utmost care was dedicated to ensure that the dosing regimens, including corticosteroid dosing equivalency, were appropriately classified as a high or a low/medium dose. Furthermore, the definitions of AECOPDs and the definitions of severity stratification of AECOPDs were verified to ensure the appropriate pooling of data.

A random effects model was selected a priori because the included studies had heterogeneous study design and baseline patients' characteristics.[16] Forest plots were used to illustrate the individual study findings and the random effects meta-analysis results. The I-square statistic (I^2) was used to assess for heterogeneity among the studies[17,18] and a cut-off of 50% was used to indicate statistically significant heterogeneity. The Q statistic and the p value for the Q statistic were also calculated. Dichotomous outcomes were calculated as risk ratios (RRs) with 95% confidence intervals (CIs) for the primary and secondary outcomes. Statistical analysis was conducted with R version 4.2.1 with R studio version 2022.02.3.

Certainty of Evidence

The quality of the evidence was assessed via the use of the GRADE approach and primarily based on the Risk of bias of included RCTs and calculation of heterogeneity.[19]

Results

Studies Selection and Characteristics

In total, 5448 records were screened and 296 full text articles were assessed for eligibility. Of these, 13 studies met all the inclusion criteria and were advanced to qualitative and quantitative analysis.[13,20–31] A PRISMA flow diagram with the selection process was created to depict this work (Figure 1).

Extensive information on the methodology of each study, including the type of ICS and type of ancillary broncho-dilator used, the locations where the study was performed, the primary outcomes investigated and the AECOPD definition, as well as on the baseline characteristics of their included population samples were collected. This data is presented in Table 1 and ETable 1.

Of note, all our comparisons were performed between high and medium dose of ICS combinations.

Primary Efficacy Outcome

There were 12,219 patients included in the analysis of our primary efficacy outcome. The any AECOPD risk varied substantially between the studies with the risk for the high dose ranging from 6.8% to 48% and for the medium dose from

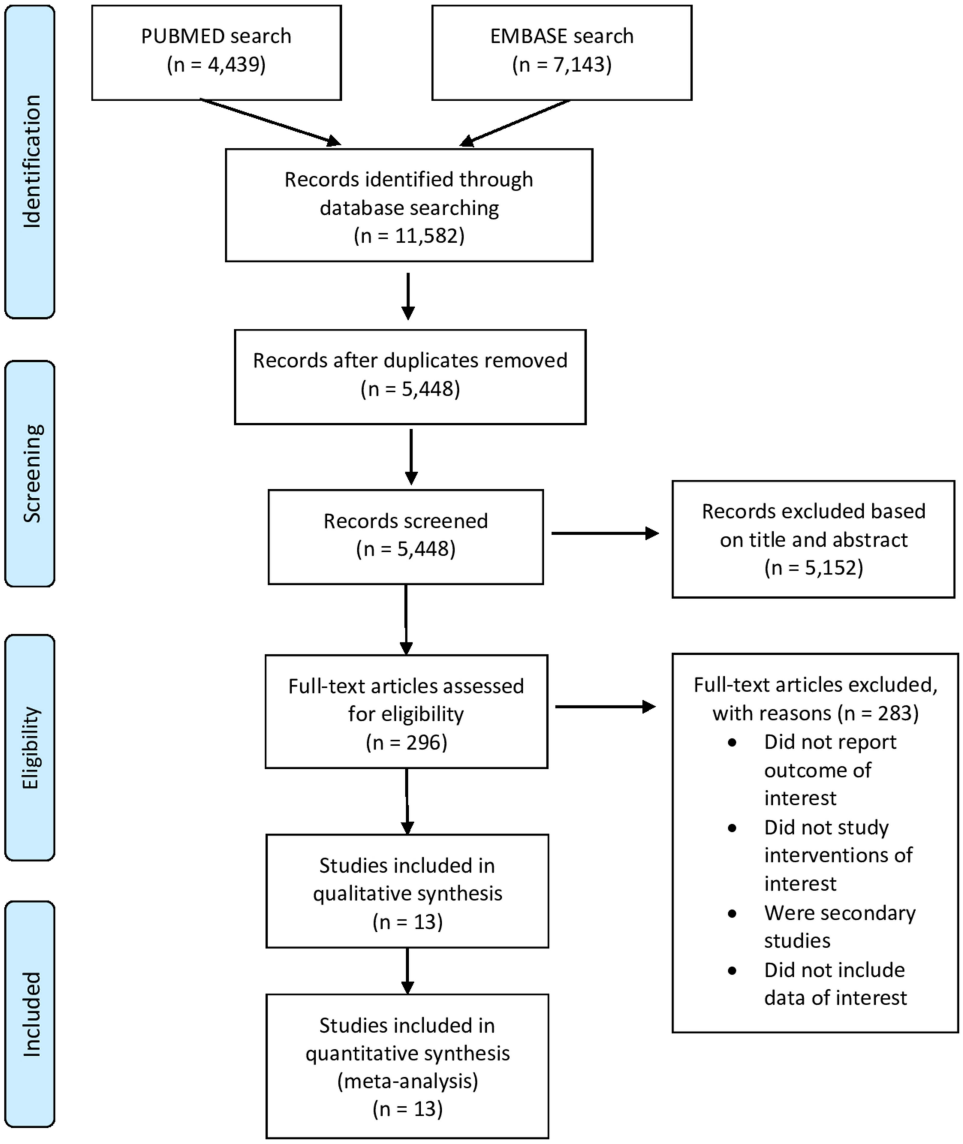

Figure 1 PRISMA Flowchart.

6.4% to 47.8%. Cumulatively, no statistically significant difference was identified between the high and medium dose ICS groups (RR: 0.98, 95% CI: 0.91–1.05, I^2: 41.3%) (Figure 2).

The certainty of evidence for this comparison was calculated to be "Moderate" because of low risk of bias of included RCTs, low-to-intermediate heterogeneity among the included studies and thus low-to-intermediate inconsistency and absence of imprecision.

Primary Safety Outcome

There were 13,557 patients included in the analysis of our primary safety outcome. The mortality rate was low in all studies and a relatively high variability was appreciated with mortality for the high dose ranging from 0.5% to 3.8% and for the medium dose from 0.3% to 3.2%. Cumulatively, no statistically significant mortality difference was identified between the high and medium dose ICS groups (RR: 0.99, 95% CI: 0.75–1.32, I^2: 0.0%) (Figure 3).

The certainty of evidence for this comparison was calculated to be "Low" because of low risk of bias of included RCTs, low heterogeneity among the included studies, absence of inconsistency but moderate possibility of imprecision as per few deaths in each study.

Table 1 Baseline Characteristics of Study Populations in the Included RCTs

Study	(N of Males)	Follow-up Time	High Dose ICS	Medium Dose ICS	Ancillary Medication	Age High/ Medium Dose *	PY High/ Medium Dose *	Mean FEV1 High/ Medium Dose	N with GOLD 2–4 High/ Medium Dose	N with recent M/S AE High/ Medium Dose
Cheng et al, 2014[20]	106(92)/ 111(93)	52 weeks	Fluticasone Propionate 1000µg/ day	Fluticasone Propionate 500µg/day	Salmeterol	66.4±20.3/ 68±23.4	27.4±16.5/ 29.1±19.3	1.24/1.27	29-47-30/ 24-51-36	NA/NA
Doherty et al, 2012[21]	225(168)/239(175)	52 weeks	Mometasone 800µg/ day	Mometasone 400µg/ day	Formoterol	59.2±9.1/ 60.1 ±9.0/	54.8±186.4/ 40.3±26.2	NA/NA	NA/NA	NA/NA
Dransfield et al, 2013[22]	402(249), 409(218)/ 403(231), 403(222)	52 weeks	Fluticasone Furoate 200 µg/day	Fluticasone Furoate 100 µg/day	Vilanterol	63.8±9.3, 63.5 ±8.8/ 63.6±9.1, 64.0±9.3	NA/NA	1.3–1.3/1.3–1.3	NA/NA	402–409/403–403
Ferguson et al, 2018[23]	655(402)/637(377)	24 weeks	Budesonide 640µg/ day	Budesonide 320µg/day	Formoterol	64.2±7.7/64.3 ±7.6/	44.7±23.5/ 44.7±22.1	1.548/1.532	NA/NA	168/188
Hanania et al, 2020[24]	619(367)/617(345)	12 to 52 weeks	Budesonide 640µg/ day	Budesonide 320µg/day	Formoterol	65.3±8.1/64.5 ±8.4/	44.2±26.0/ 45.8±28.0	NA/NA	338-241-37/330-230-56	614/616
Martinez et al, 2013[25]	205(137)/204(144)	24 weeks	Fluticasone Furoate 200 µg/day	Fluticasone Furoate 100 µg/day	Vilanterol	61.1±8.6/61.9 ±8.8/	41.5±23.4/ 42.8±23.9	1.458/1.491	NA/NA	53/50
Papi et al, 2017[26]	587(443)/588(427)	52 weeks	Fluticasone Propionate 1000µg/ day	Fluticasone Propionate 500µg/day	Formoterol	63.8±7.9/63.0 ±7.8/	39.1±19.5/ 39.2±20.1	1.03/1.02	NA/NA	NA/NA
Rabe et al, 2020[13]	2137(1260)/ 2121(1298)	52 weeks	Budesonide 640µg/ day	Budesonide 320µg/day	Glycopyrrolate and Formoterol	64.6±7.6/ 64.6±7.6/	47.0±25.1/47.9 ±25.8	NA/NA	NA/NA	2135/ 2119
Rennard et al, 2009[27]	494(308)/494(310)	12 months	Budesonide 640µg/ day	Budesonide 320µg/day	Formoterol	63.2±8.9/63.6 ±9.2/	40**/40**	1.00/1.00	84-290-120/ 85-314-94	NA/NA
Sharafkhaneh et al, 2012[28]	407(262)/408(264)	12 months	Budesonide 640µg/ day	Budesonide 320µg/day	Formoterol	63.8±9.4/62.8 ±9.2/	46**/44**	1.01/1.02	NA/NA	163/165
Tashkin et al, 2008[30]	277(188)/281(181)	6 months	Budesonide 640µg/ day	Budesonide 320µg/day	Formoterol	63.1±9.0/63.6 ±9.0/	40**/40**	1.04/1.04	NA/NA	NA/NA
Tashkin et al, 2012[29]	217(171)/207(161)	52 weeks	Mometasone 800µg/ day	Mometasone 400µg/day	Formoterol	59.7±9.1/60.9 ±8.1/	39.7±28.4/41.7 ±43.4	NA/NA	NA/NA	NA/NA
Zheng et al, 2015[31]	160(145)/161(144)	24 weeks	Fluticasone Furoate 200 µg/day	Fluticasone Furoate 100 µg/day	Vilanterol	62.7±8.7/65.1 ±9.2/	37.4±22.2/39.0 ±22.2	1.064/1.096	NA/NA	41/42

Notes: *Data presented in Mean±SD form, **Number represents Median instead of Mean.
Abbreviations: N, Number; PY, Pack Year History; NA, Not available.

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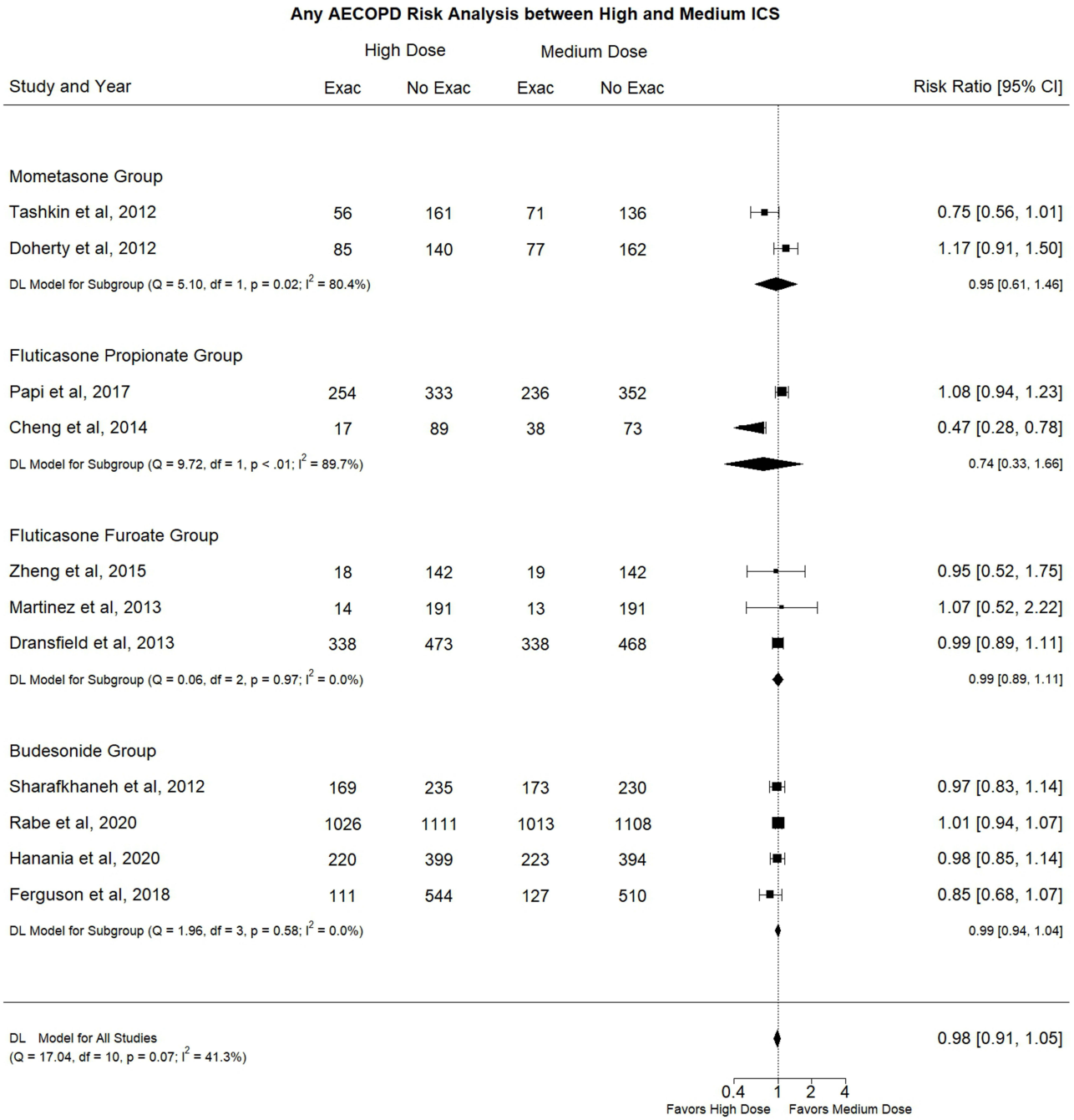

Figure 2 Comparison of Any AECOPD Risk between patients with COPD using High Dose ICS versus Medium ICS as part of maintenance therapy.

Secondary Efficacy Outcome

There were 11,190 patients included in the analysis of our secondary efficacy outcome. The moderate or severe AECOPD risk varied substantially between the studies with the risk for the high dose ranging from 6.8% to 48% and for the medium dose from 6.4% to 47.8%. Cumulatively, no statistically significant difference was identified between the high and medium dose ICS groups (RR: 1.01, 95% CI: 0.96–1.06, I^2: 0.0%) (Figure 4).

The certainty of evidence for this comparison was calculated to be "High" because of low risk of bias of included RCTs, low heterogeneity among the included studies, absence of inconsistency or imprecision.

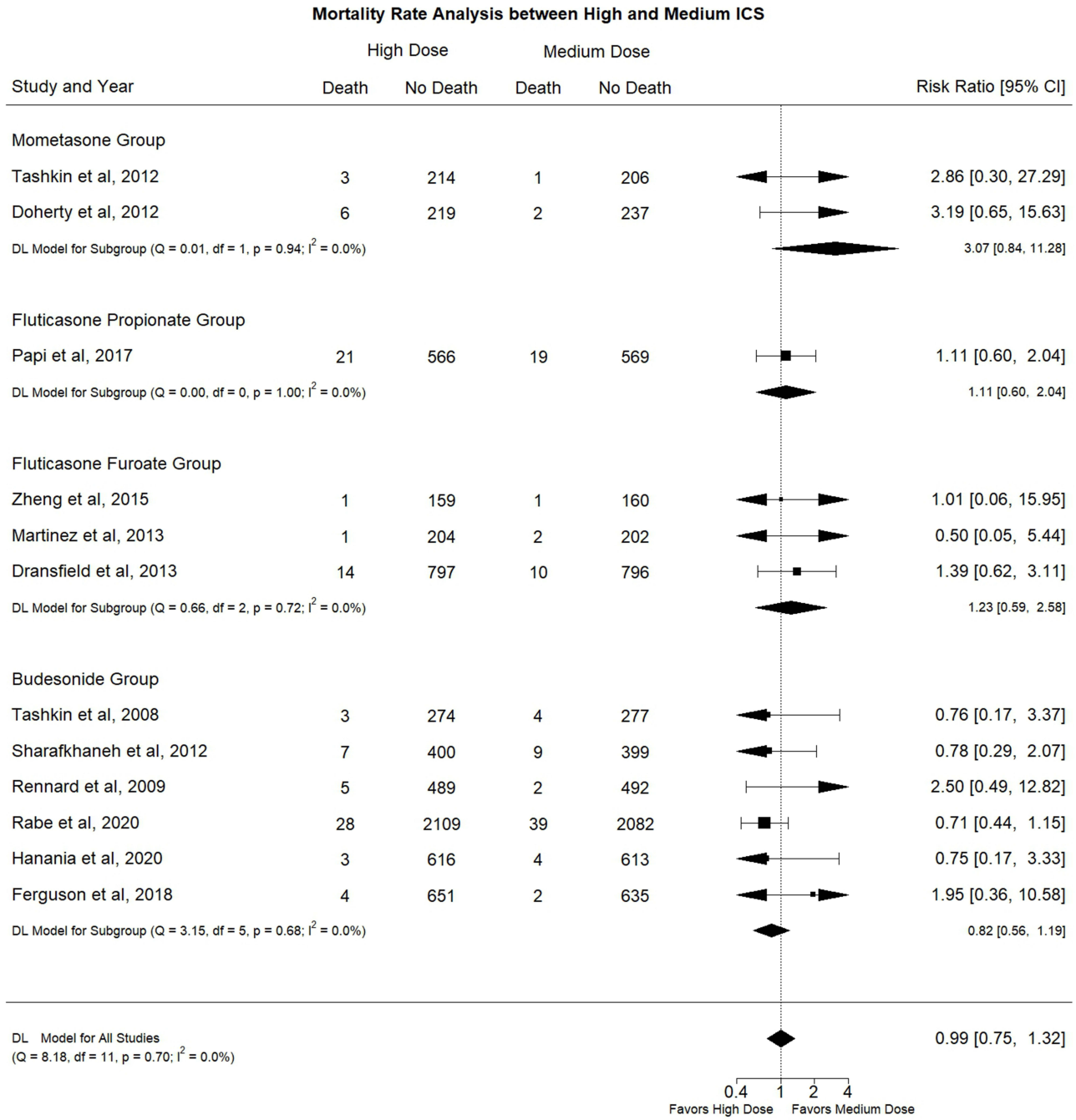

Figure 3 Comparison of Mortality Risk Rate between patients with COPD using High Dose ICS versus Medium ICS as part of maintenance therapy.

Secondary Safety Outcome

There were 13,567 patients included in the analysis of our secondary safety outcome. The pneumonia risk also varied substantially between the studies with the risk for the high dose ICS ranging from 0.7% to 8.0% and for the medium dose from 0.4% to 7.2%. Cumulatively, no statistically significant difference was identified between the high and medium dose ICS groups (RR: 1.07, 95% CI: 0.86 −1.33, I^2: 9.3%) (Figure 5).

The certainty of evidence for this comparison was calculated to be "Moderate" because of low risk of bias of included RCTs, low heterogeneity among the included studies and thus low-to-intermediate inconsistency and absence of imprecision.

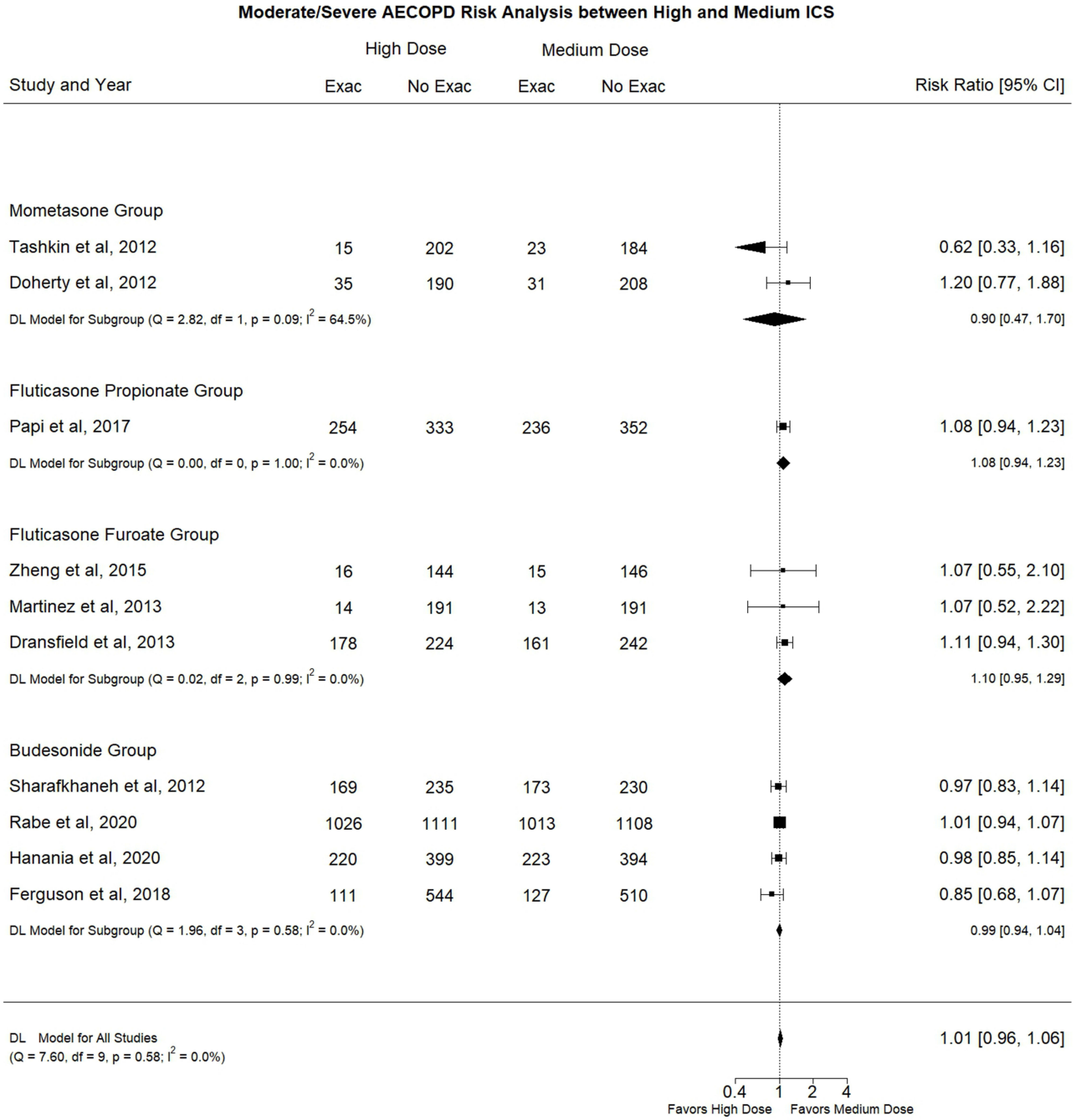

Figure 4 Comparison of Moderate/Severe AECOPD Risk between patients with COPD using High Dose ICS versus Medium ICS as part of maintenance therapy.

Type of Inhaled Corticosteroid Subgroup

When focusing on separate inhaled corticosteroids agents, the high dose of mometasone was not associated with a statistically significant difference in any AECOPD risk (2 studies, RR: 0.95, 95% CI: 0.61–1.46, I^2: 80.4%), mortality rate (2 studies, RR: 3.07, 95% CI: 0.84–11.28, I^2: 0.0%), moderate/severe AECOPD risk (2 studies, RR: 0.90, 95% CI: 0.47–1.70, I^2: 64.5%), pneumonia risk (2 studies, RR: 2.20, 95% CI: 0.76–6.37, I^2: 0.0%) compared to the medium dose of mometasone. (Figures 2–5) The certainty of evidence was calculated as "Low" for the ones with low heterogeneity and "Very Low" for the ones with high heterogeneity.

The high dose of fluticasone propionate was not associated with a statistically significant difference in any AECOPD risk (2 studies, RR: 0.74, 95% CI: 0.33–1.66, I^2: 89.7%), mortality rate (1 study), moderate/severe AECOPD risk (1

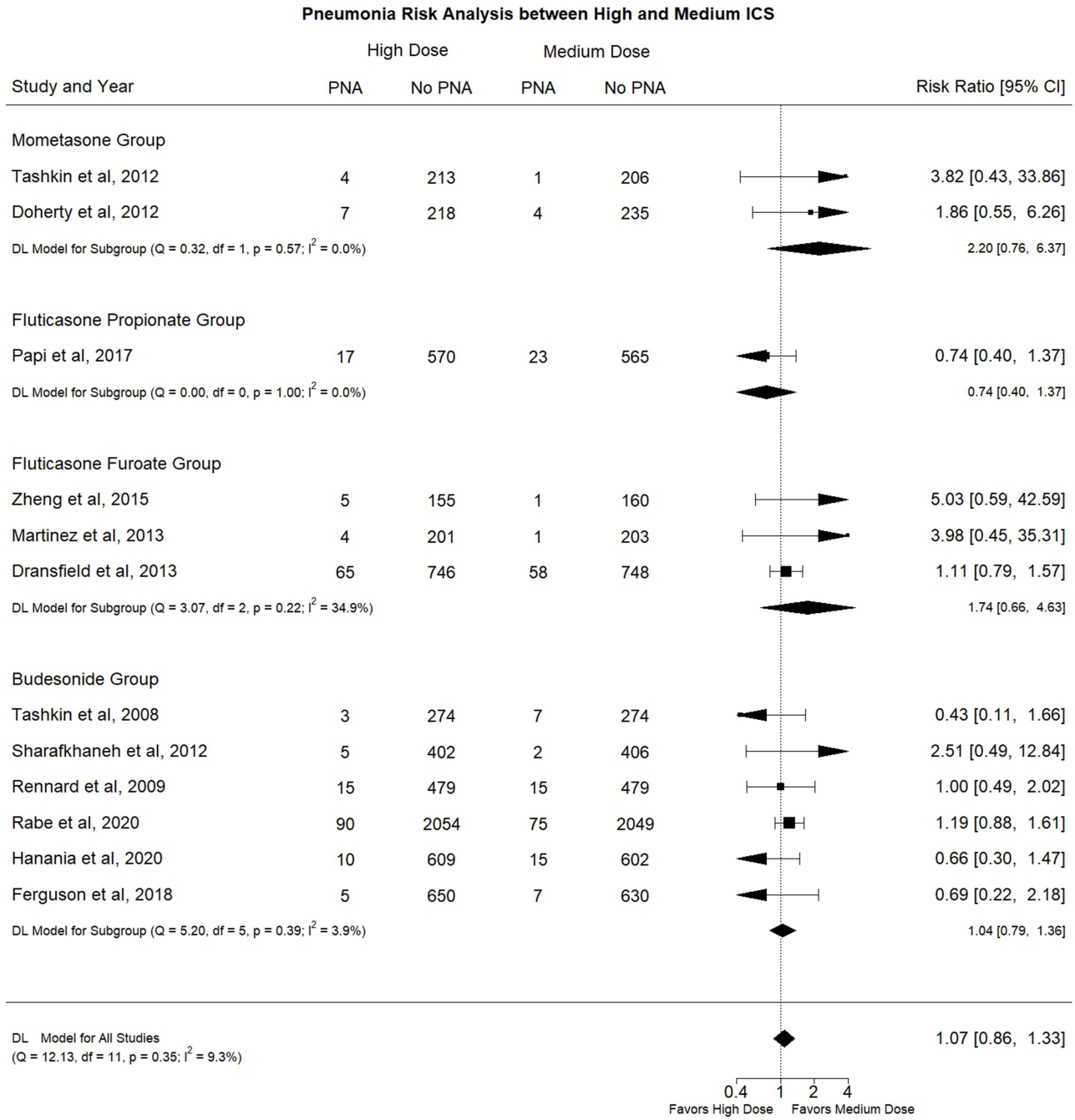

Figure 5 Comparison of Pneumonia risk between patients with COPD using High Dose ICS versus Medium ICS as part of maintenance therapy.

study) or pneumonia risk (1 study) compared to the medium dose of fluticasone propionate (Figures 2–5). The certainty of evidence for the one comparison was calculated as "Very Low" as per high heterogeneity.

The high dose of fluticasone furoate was not associated with a statistically significant difference in any AECOPD risk (3 studies, RR: 0.99, 95% CI: 0.89–1.11, I^2: 0.0%), mortality rate (3 studies, RR: 1.23, 95% CI: 0.59–2.58, I^2: 0.0%), moderate/severe AECOPD risk (3 studies, RR: 1.10, 95% CI: 0.95–1.29, I^2: 0.0%) or pneumonia risk (3 studies, RR: 1.74, 95% CI: 0.66–4.63, I^2: 34.9%) compared to the medium dose of fluticasone furoate (Figures 2–5). The certainty of evidence was calculated as "High" for any and moderate/severe AECOPD comparisons and "Low" for the Mortality and pneumonia comparisons as per low documented counts.

Finally, the high dose of budesonide was not associated with a statistically significant difference in any AECOPD risk (4 studies, RR: 0.99, 95% CI: 0.94–1.04, I^2: 0.0%), mortality rate (6 studies, RR: 0.82, 95% CI: 0.56–1.19, I^2: 0.0%), moderate/severe AECOPD risk (4 studies, RR: 0.99, 95% CI: 0.94–1.04, I^2: 0.0%) or pneumonia risk (6 studies, RR: 1.04, 95% CI: 0.79–1.36, I^2: 3.9%) compared to the medium dose of budesonide (Figures 2–5). The certainty of evidence was calculated as "High" for any and moderate/severe AECOPD comparisons, "Moderate" for pneumonia and "Low" for the mortality comparison as per low documented counts.

Patients with Moderate, Severe or Very Severe COPD Subgroup

In the subgroup of patients suffering from moderate, severe or very severe COPD, no statistically significant difference was identified between the high and medium ICS dose in any AECOPD risk (RR: 1.01, 95% CI: 0.94–1.07, I^2: 22.5%), mortality rate (RR: 0.93, 95% CI: 0.68–1.28, I^2: 0.0%), moderate/severe AECOPD risk (RR: 1.01, 95% CI: 0.96–1.06, I^2: 0.0%) or pneumonia risk (RR: 1.02, 95% CI: 0.77–1.36, I^2: 13.83%). (EFigure 1A–D) The certainty of evidence was calculated as "High" for any, moderate/severe AECOPD and pneumonia comparisons and "Low" for the mortality comparison as per low documented counts.

Patients with Recent Exacerbation Subgroup

In the subgroup of patients with recent AECOPD, no statistically significant difference was identified between the high and medium ICS dose in any AECOPD risk (RR: 1.00, 95% CI: 0.95–1.00, I^2: 0.0%), mortality rate (RR: 0.88, 95% CI: 0.61–1.26, I^2: 0.0%) or moderate/severe AECOPD risk (RR: 1.01, 95% CI: 0.96–1.06, I^2: 0.0%) or pneumonia risk (RR: 1.11, 95% CI: 0.91–1.37, I^2: 0.0%). (EFigure 2A–D) The certainty of evidence was calculated as "High" for any, moderate/severe AECOPD and pneumonia comparisons and "Low" for the mortality comparison as per low documented counts.

Publication Bias

Funnel plots were constructed for all outcomes and no major evidence of publication bias was appreciated. These Funnel plots are presented in EFigure 3A–L.

Other Risks of Bias Assessment

Our risk of bias assessment was based on the appropriate tool, RoB2 for RCTs, and did not reveal any major source of bias for any of the included studies (EFigure 4).

Discussion

This study was a systematic review and meta-analysis of 13 RCTs comparing the efficacy and safety profile of two different dosage levels (high versus medium) of ICS in combination with at least one bronchodilator (LABA, LAMA or both) in COPD.

Assessing the methodology of the included studies, a significant alignment is appreciated. Initially, there is agreement on the specific ICS dosing between studies using the same ICS and on the dosing equivalency between studies using different agents. Second, there are significant similarities in the methodology of patient population selection and of outcome assessment, including their definitions of AECOPD and AECOPD severity levels. Third, the investigational period is deemed relatively similar between studies and generally spanning from 6 to 12 months. All in all, our decision to pool the results of the studies is deemed methodologically appropriate.

Our results indicate that i) the use of high dose ICS was not associated with a statistically significant difference in any AECOPD risk, ii) the use of high dose ICS was not associated with a statistically significant difference in mortality rate, iii) the use of high dose ICS was not associated with a statistically significant difference in moderate or severe AECOPD risk, iv) the use of high dose ICS was not associated with a statistically significant difference in pneumonia risk, v) no difference on any AECOPD risk, mortality rate, moderate/severe AECOPD risk or pneumonia risk was identified with individual ICS agent subgroup analysis, vi) no difference on any AECOPD risk, mortality rate, moderate/severe AECOPD risk or pneumonia risk was identified with patients suffering from moderate, severe or very severe COPD

subgroup analysis, vii) no difference on any AECOPD risk, mortality rate, moderate/severe AECOPD risk or pneumonia risk was identified with patients with recent AECOPD history subgroup analysis.

Our results provide a possibly significant contribution to the decision-making process of clinicians providing care to patients with COPD. According to the most recent GOLD guidelines,[3] one of the main treatment goals for these patients is to tailor their inhaler maintenance regimen to prevent AECOPD, as per their multilevel detrimental effects.[32,33] Combined ICS and bronchodilator therapy has been associated with improvement in lung function and health status as well as reduction in exacerbations.[3] Additionally, ICS combinations have been associated with all-cause mortality benefit. Two recent large RCTs (IMPACT and ETHOS) showed reduction in all-cause mortality when ICS is added to dual bronchodilator therapy relative to dual bronchodilation therapy alone.[34,35] The same conclusion was reached by a recently published meta-analysis that investigated all-cause mortality as the primary outcome.[12] Finally, it is important to mention the effect of ICS combinations on cardiovascular events. Again, the IMPACT trial identified a reduced risk of cardiovascular mortality and the ETHOS trial identified a reduced risk for major adverse cardiovascular events. However, it is important to underline that the effect was not corroborated by the equally large and oriented to cardiovascular events SUMMIT trial.[11] According to the above and pending further elaboration, COPD guidelines suggest adding ICS in patients with a history of COPD-related hospitalization, ≥2 moderate exacerbations the last year, blood eosinophil counts >300 cells/μL, and/or a history of asthma.[3]

Despite the aforementioned and significant benefits, ICS use has been linked with several safety concerns and thus ICS use is not recommended in patients with low eosinophil counts (<100 cells/μL), history of mycobacterial infection, and those with several pneumonias.[3] Elaborating on these concerns, the risk of pneumonia development with the use of this medication class has been investigated by RCTs, with the majority identifying an increased risk[22,26,28,36–38] and a minority a similar risk,[4,21,27,29] by observational studies[39] and by meta-analyses of RCTs, with the majority again identifying an increased risk[40–42] and a minority a similar risk.[43] Second, the risk of onset or deteriorated control of Diabetes Mellitus has been associated with ICS use. Evidence of such effect has been demonstrated by both randomized and observational studies[28,44] but a significant number of studies have been unable to prove a difference.[13,20,30,45–47] Finally, ICS have been associated with deleterious effects on bone health (either decreased bone density or fractures) with mixed results from different studies once again with some studies identifying deleterious effects[22,27] while others not identifying a connection.[13,21,48,49] As per the above, a significant level of ambiguity is appreciated with the adverse effects linked to ICS use. In this setting and considering the dose-dependent nature of some of these side effects,[9,10] the use of the lowest possible dose of ICS becomes very clinically relevant. As a consequence, our study provides pertinent information on the appropriate dosing of ICS by assessing the benefits and detriments of the different dosing levels.

Strengths and Weaknesses

Our study demonstrates a number of strengths. Specifically, we strictly adhered to the systematic review methodology from start to finish, we narrowly focused on one primary efficacy, one primary safety, one secondary efficacy and one secondary safety outcome avoiding a more nebulous spectrum of outcomes. Second, these outcomes were identified as clinically relevant for all practitioners providing care to patients with COPD and as unambiguous in nature thus avoiding introduction of bias to our study. Third and because of this methodology, we were able to search, collect, screen and analyze a significant number of studies and thus a substantial patient population size.

Our study demonstrates certain weaknesses as well. First, our goal to pool low and medium dose was not achieved as all included studies used the medium dose of respective ICS and none used the low dose. Second, we considered 640mcg/day and 320mcg/day of budesonide as high and low/moderate dose respectively based on US regulatory labelling although these doses have been categorized as medium and low by other organizations.[50] Alongside the budesonide dosing intensity topic, the approved ICS doses in the United States reach medium intensity only, most high doses of ICS are not used even in a RCT setting and thus the possibility of region-specific results is introduced in our study. Third, the methods used to identify, quantify, and present AECOPD in our source material were not uniform. Although data on the outcome were available in all of them, it was impossible in some cases to use it because we were unable to mathematically convert it to our statistic of choice, such as when extracting COPD exacerbations per person-year. On the other hand, some studies did not provide data on all severity levels of exacerbation and instead focused on

the most clinically relevant moderate or severe ones. In this scenario, we included these counts in our primary outcome. Finally, we did not investigate the contribution of eosinophil count measurement to the effect of the dosing levels on the outcomes of choice, a research point of interest recently.

Conclusion

The high ICS dose combined with bronchodilator therapy neither reduces AECOPD and mortality rates nor increases pneumonia risk relative to the medium dose. Further research might be needed to investigate whether low ICS doses can provide similar benefits with fewer adverse events than medium or high ICS doses to patients with COPD.

IRB Review

This study is a review and meta-analysis, which does not require IRB review.

Data Sharing Statement

Our data is derived from public domain resources. All data source material that supports the findings of this study are available on Medline and Embase.

Author Contributions

PAB was involved in the study execution, data analysis and data interpretation and was involved in the manuscript drafting and writing.

TT was involved in the study design, study execution and acquisition of data and was involved in substantially revising the article.

JYY, GJHR and VG were involved in the study execution, acquisition of data and were involved in substantially revising the article.

FJM was involved in the study conception, data (result) interpretation and was involved in substantially revising and critically reviewing the article.

SF was involved in the study conception, study design, study execution and was involved in article writing, substantially revising and critically reviewing the article.

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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