



# Inhaled Corticosteroids and the Pneumonia Risk in Patients With Chronic Obstructive Pulmonary Disease: A Meta-analysis of Randomized Controlled Trials

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Chen H, Sun J, Huang Q, Liu Y, Yuan M, Ma C and Yan H (2021) Inhaled Corticosteroids and the Pneumonia Risk in Patients With Chronic Obstructive Pulmonary Disease: A Meta-analysis of Randomized Controlled Trials. Front. Pharmacol. 12:691621. doi: 10.3389/fphar.2021.691621 **Background:** Whether all types of inhaled corticosteroids (ICSs) would increase the pneumonia risk in patients with chronic obstructive pulmonary disease (COPD) remains controversial. We aimed to assess the association between ICSs treatment and pneumonia risk in COPD patients, and the impact of medication details and baseline characteristics of patients on the association.

**Methods:** Four databases (PubMed, Embase, Cochrane Library, and Clinical Trials.gov) were searched to identify eligible randomized controlled trials (RCTs) comparing ICSs treatment with non-ICSs treatment on the pneumonia risk in COPD patients. Pooled results were calculated using Peto odds ratios (Peto ORs) with corresponding 95% confidence intervals (CIs).

**Results:** A total of 59 RCTs enrolling 103,477 patients were analyzed. All types of ICSs significantly increased the pneumonia risk (Peto OR, 1.43; 95% Cl, 1.34–1.53). Subgroup analysis showed that there was a dose-response relationship between ICSs treatment and pneumonia risk (low-dose: Peto OR, 1.33; 95% Cl, 1.22–1.45; medium-dose: Peto OR, 1.50; 95% Cl, 1.28–1.76; and high-dose: Peto OR, 1.64; 95% Cl, 1.45–1.85). Subgroup analyses based on treatment durations and baseline characteristics (severity, age, and body mass index) of patients were consistant with the above results. Subgroup analysis based on severity of pneumonia showed that fluticasone (Peto OR, 1.75; 95% Cl, 1.44–2.14) increased the risk of serious pneumonia, while budesonide and beclomethasone did not.

**Conclusions:** ICSs treatment significantly increased the risk of pneumonia in COPD patients. There was a dose-response relationship between ICSs treatment and pneumonia risk. The pneumonia risk was related with COPD severity.

Keywords: inhaled corticosteroids, chronic obstructive pulmonary disease, adverse event, pneumonia, metaanalysis

# INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is currently the third leading cause of death in the world, and acute exacerbations contribute substantially to this (GBD 2015 Chronic Respiratory Disease Collaborators, 2017; Viniol and Vogelmeier, 2018; López-Campos et al., 2019). Treatment and prevention of repeated exacerbations have been identified as a priority by the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Currently, the management of patients with stable COPD mainly relies on inhaled agents such as inhaled corticosteroids (ICSs), long-acting muscarinic antagonist (LAMA), long-acting  $\beta$ -agonist (LABA), etc. Among them, ICSs have been recommended by GOLD as first-line maintenance treatment in patients with repeated exacerbations to relieve the frequency and severity of acute exacerbations of COPD, and improve their quality of life (Yang et al., 2017).

Some recent studies have raised concerns about increased pneumonia risk associated with long-term use of ICSs (Dong et al., 2014; Kew and Seniukovich, 2014; Morjaria et al., 2017; Janson et al., 2018; Yang et al., 2019; Zhang et al., 2020). However, the association between various types of ICSs and the pneumonia risk remains controversial, as the conclusions of the previous published meta-analyses are different (Sin et al., 2009; Singh et al., 2009; Kew and Seniukovich, 2014; Festic et al., 2016; Yang et al., 2019). However, the reliability and generalizability of these studies might be weakened by their small sample size, since a large number of important randomized controlled trials (RCTs) after 2017 were not included in these meta-analyses (Bhatt et al., 2017; Papi et al., 2017; Siler et al., 2017; Vestbo et al., 2017; Betsuyaku et al., 2018; Chapman et al., 2018; Ferguson et al., 2018a, Ferguson et al., 2018b; Frith et al., 2018; Lipson et al., 2018; Papi et al., 2018; Ichinose et al., 2019; Kerwin et al., 2019; Rabe et al., 2020). Moreover, none of these studies assessed the difference in the pneumonia risk in COPD patients with different demographic characteristics (including severity of airflow limitation, age, body mass index [BMI], etc.).

The aim of this meta-analysis was to objectively reappraise the pneumonia risk and serious pneumonia associated with various types of ICSs in COPD patients through all available RCTs. We also aimed to assess the impact of medication details (including dosage level and treatment duration) and demographic characteristics (severity, age, and body mass index) of patients on this association.

## METHODS

## **Protocol and Guidance**

This meta-analysis was carried out according to the Preferred Reporting Items for Systematic review and Meta-Analysis (Moher et al., 2009). Ethics committee approval is not applicable for this meta-analysis. The study was registered with PROSPERO prospectively (#CRD42020213586).

## Search Strategy

Two reviewers (Hong Chen and Jian Sun) independently searched the databases of PubMed, Embase, Cochrane

Library, and Clinical Trials.gov from inception until February 2021, using the following terms: ("chronic obstructive pulmonary disease" OR "COPD" OR "pulmonary disease, chronic obstructive" or "chronic obstructive airway disease" OR "airflow obstruction, chronic" OR "chronic airflow obstruction" OR "chronic obstructive lung disease" OR "emphysema" OR "Bronchitis") AND ("inhaled corticosteroids" OR "ICS" OR "budesonide" OR "fluticasone" OR "mometasone" OR "beclomethasone" OR "triamcinolone" OR "ciclesonide"). Articles in English were included. Disagreements regarding eligibility were resolved by discussion by two investigators and, if necessary, consultation with a third investigator (Hao Yan).

## **Eligibility Criteria**

We included eligible studies based on the PICOS (Participants [P], Interventions [I], Comparators [C], Outcomes [O], and Study design [S]) criteria (Shamseer et al., 2015): 1) Participants: patients aged 40 yr or over, with stable, moderate (GOLD stage II) to very severe (GOLD stage IV) COPD. Patients with other respiratory diseases, such as asthma, bronchiectasis were excluded. 2) Interventions: various types and doses of ICSs as the intervention treatment. 3) Comparisons: non-ICSs treatment as a control treatment. 4) Outcome: Pneumonia for this meta-analysis was defined as an adverse event based on the Medical Dictionary for Regulatory Activities (MedDRA, version 10.0)pneumonia-related preferred terms, including "pneumonia," "lobar pneumonia," "bronchopneumonia," "pneumonia pneumococcal," or "pneumonia staphylococcal" (Rennard et al., 2009; Sin et al., 2009). One or more of the above MedDRA terms reported in the adverse events list or the safety profiles by the RCTs would be identified as pneumonia data, and included in our analysis. Serious pneumonia was defined as a pneumonia leading to mechanical ventilation or death, or requiring hospital admission (Aaron et al., 2007; Pascoe et al., 2015). 5) Study design: only RCTs were included. Non-RCTs, such as retrospective studies, reviews, case reports and case-control studie, were excluded.

## **Data Extraction and Quality Assessment**

Two reviewers (Qiang Huang and Yongqi Liu) independently identified references and extracted data from eligible RCTs. Any disagreements would be resolved by discussion to reach a consensus, and consulted a third reviewer if necessary. The risk of bias of the included RCTs was assessed by two independent reviewers (Hong Chen and Mengxin Yuan) using the Cochrane risk of bias tool (Higgins et al., 2011). Any disagreements would be resolved by discussion and consultation (Hao Yan).

## **Subgroup Analyses**

Subgroup analyses were conducted based on: 1) types of ICSs (fluticasone, budesonide, mometasone furoate and beclomethasone); 2) doses of ICSs (low-dose [defined as  $100-250 \mu$ g/d of fluticasone propionate or equivalent], medium-dose [defined as >250-500  $\mu$ g/d of fluticasone propionate or equivalent], and high-dose [defined as



>500 µg/d of fluticasone propionate or equivalent]); 4) treatment durations (short-term ICSs treatment [defined as  $\leq 6 \text{ mo}$ ] and long-term ICSs treatment [defined as >6 mo]); 5) severity (moderate COPD [GOLD stage II], severe COPD [GOLD stage III] and very severe COPD [GOLD stage IV]); 6) age of patients (<65 yr old and  $\geq 65 \text{ yr old}$ ); 7) body mass index (BMI) of patients ( $\geq 25 \text{ and } < 25$ ).

## **Statistical Analysis**

The Review Manager 5.3 software was used to calculate the pooled results. Considering Peto odds ratio (Peto OR) could provide the best confidence interval (CI) when events are rare (Bradburn et al., 2007), the pooled results for the comparison of ICSs treatment vs non-ICSs treatment were calculated using Peto ORs. Sensitivity analysis was performed after excluding those studies with high risk of bias. Subgroup analyes based on the baseline demographic characteristics (severity, age, and

body mass index) of the patients were conducted using the individual patient level data, which was extracted from the baseline data of the included RCTs (mean or median for lung function, age and BMI). This method of analyzing the individual patient level data was used by Sobieraj et al. (Sobieraj et al., 2018) previously. A two tailed *p*-value <0.05 was considered to be statistically significant. Statistical heterogeneity was further measured using the I<sup>2</sup> test, and I<sup>2</sup>  $\geq$ 50% indicated a substantial heterogeneity (Higgins et al., 2003).

# RESULTS

## **Eligible Trials and Study Descriptions**

Our search identified 4,595 citations. After evaluating these citations, we included 59 RCTs (Vestbo et al., 1999; Burge

### TABLE 1 | Detailed characteristics of the included randomized controlled trials.

	Age, y		chodilator FEV <sub>1</sub> (%	use, Pack-years		months	μg	incidence	pneumonia incidence
			predicted)					Events/ Patients	Events/ Patients
Vestbo et al.	ICS: 59	ICS: 58.6	ICS: 86-2	NR	NR	36	ICS: BUD 400 bid	ICS: 16/145	NR
(1999)	CP: 59.1	CP: 62.1	CP: 86-9		100 015		CP: P	CP: 24/145	100 10/070
Burge et al.	ICS: 63.8	ICS: 75.4	ICS: 50	44	ICS: 24.5	36	ICS: FP 500 bid	ICS: 20/376	ICS: 16/370
(2000)	CP: 63.7	CP: 75	CP: 50.3	100.00	CP: 24.9	10	CP: P	CP: 9/375	CP: 8/368
Calverley et al. (2003)	ICS: ≥40	ICS: 76	36	ICS: 39	NR	12	ICS: BUD/FM 320/9 bid; BUD 400 bid	ICS: 13/511	NR
	CP: ≥40	CP: 75	100 00 5	CP: 38.5		10	CP: FM 9 bid; P	CP: 9/511	
Szafranski et al.	ICS: 64	ICS: 78	ICS: 36.5	ICS: 44	NR	12	ICS: BUD 160/4.5 bid	ICS: 6/208	NR
(2003)	CP: 65	CP: 79.5	CP: 36	CP: 45			CP: FM 4.5 bid; P	CP: 9/205	
Aaron et al.	ICS: 67.8	ICS: 57.9	ICS: 42.2	ICS: 50.3	ICS: 27.8	12	ICS: SFC 250/25 bid	ICS: 1/145	ICS: 1/145
(2007)	CP: 67.9	CP: 56.6	CP: 41.6	CP: 50.3	CP: 27.4		CP: S	CP: 1/304	CP: 1/304
Calverley et al.	ICS: 65	ICS: 75	ICS: 44.2	ICS: 48.1	ICS: 25.4	36	ICS: SFC 500/50 bid;	ICS: 217/	NR
(2007)	CP: 65.1	CP: 76	CP: 43.9	CP: 49	CP: 25.4		FP 500 bid CP: S 50 bid; P	3098 CP: 124/	
								3086	
Kardos et al.	ICS: 63.8	ICS: 74	ICS: 40.4	ICS: 36.8	NR	10	ICS: SFC 500/50 bid	ICS: 23/507	NR
(2007)	CP: 64	CP: 77.6	CP: 40.3	CP: 37			CP: S 50 bid	CP: 7/487	
Calverley et al.	ICS: 65	ICS: 68	ICS: 46.5	NR	ICS: 26.4	12	ICS: MF 800 qd	ICS: 25/616	NR
(2008)	CP: 65	CP: 69	CP: 47		CP: 27.1		CP: P	CP: 6/295	
Ferguson et al.	ICS: 64.9	ICS: 58	ICS: 39.8	ICS: 58.5	ICS: 27.3	12	ICS: SFC 250/25 bid	ICS: 29/394	ICS: 19/394
(2008)	CP: 65.0	CP: 52	CP: 40.6	CP: 54.4	CP: 27.7		CP: S 25 bid	CP:15/388	CP: 10/388
Tashkin et al. (2008)	ICS: 63.3	ICS: 68.6	ICS: 39.4	ICS: 40.8	NR	6	ICS: BUD/FM 320/9 bid; BUD 160/9 bid	ICS: 8/1120	ICS: 8/1120
(2000)	CP: 63.4	CP: 67.3	CP: 40.4	CP: 40			CP: FM 9 bid; P	CP: 2/584	CP: 2/584
Wedzicha et al.	ICS: 64	ICS: 81	ICS: 39.1	ICS: 41.3	ICS: 20-29	24	ICS: SFC 500/50 bid	ICS: 50/658	ICS: 41/658
(2008)	CP: 65	CP: 84	CP: 39.4	CP: 39.5	CP: 20-29	27	CP: Tio 18 gd	CP: 24/665	CP: 19/665
Anzueto et al.	ICS: 65.4	ICS: 51	ICS: 41.2	ICS: 57.8	ICS: 27.6	12	ICS: SFC 250/25 bid	ICS: 26/394	NR
						12			חאו
(2009) Democrat et el	CP: 65.3	CP: 57	CP: 40	CP: 56.5	CP: 27.3	10	CP: S 25 bid	CP: 10/403	
Rennard et al. (2009)	ICS: 63.4	ICS: 62.6	ICS: 39.1	40	NR	12	ICS: BUD/FM 320/9 bid; BUD/FM 160/9 bid	ICS:30/988	NR
	CP: 62.9	CP: 65.3	CP: 40	100.00	100.00.0		CP: FM 9 bid; P	CP: 40/976	
Welte et al. (2009)	ICS: 62.5	ICS: 76	ICS: 38.1	ICS: 36	ICS: 26.4	3	ICS: BUD/FM 320/9 bid + Tio 18 qd	ICS: 3/331	NR
	CP: 62.4	CP: 74	CP: 37.7	CP: 38	CP: 26.3		CP: Tio 18 qd + P	CP: 3/329	
Calverley et al. (2010)	ICS: 63.5	ICS: 80.4	NR	ICS: 37.6 CP: 39.7	NR	11	ICS: BDP/FM 200/24 bid; BUD/FM 400/ 24 bid	ICS: 5/232; 7/238	NR
	CP: 63.7	CP: 81.1					CP: FM	CP: 1/233	
Dranafield at al	ICS: 63.6	ICS: 55		100, EE 0		3			NR
Dransfield et al.			ICS: 56	ICS: 55.8	ICS: 26.7	3	ICS: SFC 250/50 bid	ICS: 3/123	NR
(2011)	CP: 63.5	CP: 59	CP: 55	CP: 54.1	CP: 26.6	10	CP: P	CP: 0/126	
Doherty et al. (2012)	ICS: 60.3	ICS: 75.3	ICS: 39	ICS: 45.4	NR	12	ICS: MF/FM 400/10 bid; MF/F 200/10 bid; MF	ICS:16/717	NR
			00.001				400 bid	00.0/470	
Hanania et al.	CP: 59.2 ICS: 61.3	CP: 75 ICS: 50	CP: 38.1 ICS: 56	CP: 44.7 ICS: 55.4	ICS: 27	6	CP: FM 10 bid; P ICS: SFC250/50 bid +	CP: 6/479 ICS: 2/173	NR
(2012)							Tio 18 qd		
	CP: 61	CP: 43	CP: 57.4	CP: 54.7	CP: 27.6		CP: Tio 18 qd	CP: 0/169	
Jung et al. (2012)	ICS: 67	ICS: 97.3	ICS: 47.4	NR	ICS: 22.2	6	ICS: SFC250/50 bid + Tio 18 qd	ICS: 2/223	NR
	CP: 67.8	CP: 98.7	CP: 47.5		CP: 21.8		CP: Tio 18 qd	CP: 2/232	
Sharafkhaneh et al., 2012	ICS: ≥40	ICS: 64.6	ICS: 37.8	ICS: 45	NR	12	ICS: BUD/FM 320/9 bid; BUD/FM 160/9 bid	ICS: 45/815	NR
	CP: ≥40	CP: 56.8	CP: 37.5	CP: 43			CP: FM	CP: 11/403	
Tashkin et al. (2012a)	ICS: 60.2	ICS: 76.7	ICS: 39.2	ICS: 43	NR	12	ICS: MF/F 400/10 bid; MF/F 200/10 bid; MF	ICS: 19/1351	NR
							400 bid		
	CP: 59.3	CP: 77	CP: 38.8	CP: 42.4			CP: FM 10 bid; P	CP: 9/900	
						10	1002 ME/E 100/10 bid.		
Tashkin et al.	ICS: 60.1	ICS: 78.3	≥25 and ≤60	ICS: 40.5	NR	12	ICS: MF/F 400/10 bid;	ICS: 3/634	NR
Tashkin et al. (2012b)	ICS: 60.1	ICS: 78.3	≥25 and ≤60	ICS: 40.5	NR	12	MF/F 200/10 bid; MF 400 bid	105: 3/634	INK

(Continued on following page)

### TABLE 1 | (Continued) Detailed characteristics of the included randomized controlled trials.

Study	Mean Age, y	Male, %	Postbron- chodilator FEV <sub>1</sub> (%	Tobacco use, Pack-years	BMI	Duration, months	Interventions, µg	Pneumonia incidence	Serious pneumonia incidence
			predicted)					Events/ Patients	Events/ Patients
	CP: 59.7	CP: 76.5		CP: 40.3			CP: FM 10 bid; P	CP: 3/421	
Dransfield et al. (2013)	ICS: 63.6	ICS: 57	ICS: 45.6	NR	NR	12	ICS: FF/VI 200/25 qd; FF/VI 100/25 qd; FF/VI 50/25 qd	ICS: 154/ 2437	ICS: 71/2378
	CP: 63.8	CP: 57	CP: 45.2				CP: VI 25 qd	CP: 27/818	CP: 8/799
Fukuchi et al. (2013)	ICS: 64.5	ICS: 87.6	ICS: 40.9	ICS: 44.4	NR	3	ICS: BUD/FM 160/ 4.5 bid	ICS: 8/636	NR
	CP: 65.6	CP: 90.3	CP: 40.8	CP: 44.7			CP: FM 4.5 bid	CP: 7/657	
Kerwin et al. (2013)	ICS: 62.6	ICS: 65.7	ICS: 47.7	ICS: 45.7	NR	6	ICS: FF/VI 100/25qd; FF/VI 50/25 qd	ICS: 12/618	NR
	CP: 62.8	CP: 68	CP: 49.2	CP: 46.6		0	CP: VI 25 qd; P	CP: 8/412	
Martinez et al. (2013)	ICS: 61.7	ICS: 71.5	ICS: 47.7	ICS: 41.9	NR	6	ICS: FF/VI 200/25 qd; FF/VI 100/25 qd	ICS: 10/816	NR
Vegelmeier	CP: 61.7	CP: 74	CP: 48.4	CP: 43.9		6	CP: VI 25 qd; P	CP: 2/408	
Vogelmeier et al. (2013)	ICS: 63.2 CP: 63.4	ICS: 71.6 CP: 70.2	ICS: 60.5 CP: 60	NR	NR	6	ICS: SFC 500/50 bid CP: IND/GLY 110/50 gd	ICS: 4/264 CP: 0/258	ICS: 2/264 CP: 0/258
et al. (2013) Magnussen et al. (2014)	ICS: 63.6	ICS: 81.5	<50	NR	NR	12	ICS: SFC 500/50 bid + Tio 18 gd	ICS: 72/1243	NR
et al. (2014)	CP: 64	CP: 83.4					CP: S 50 bid + Tio 18 gd	CP: 68/1242	
Ohar et al.	ICS: 63.1	ICS: 55	ICS: 38.5	ICS: 52	ICS: 28	6	ICS: SFC 250/50 bid	ICS: 13/314	NR
(2014)	CP: 62.7	CP: 54	CP: 41.2	CP: 55.3	CP: 28.3	0	CP: S 50 bid	CP: 10/325	
Pepin et al.	ICS: 66.7	ICS: 85	ICS: 45.6	ICS: 42.6	ICS: 27.1	3	ICS: FF/VI 100/25 qd	ICS: 3/127	NR
(2014)	CP: 67.7	CP: 86	CP: 47.4	CP: 44.6	CP: 27.2		CP: Tio 18 qd	CP: 0/130	
Rossi et al.	ICS: 66.8	ICS: 68.4	ICS: 62.4	ICS: 42	NR	6	ICS: SFC 500/50 bid	ICS: 2/288	NR
(2014)	CP: 65.3	CP: 69.6	CP: 64	CP: 41.4			CP: IND/GLY 110/50 qd	CP: 0/293	
Wedzicha et al.	ICS: 64.6	ICS: 69	ICS: 41.9	ICS: 43.1	ICS: 26.5	11	ICS: BDP/FM 100/6 bid	ICS: 23/601	NR
(2014)	CP: 63.9	CP: 69	CP: 41.6	CP: 42.7	CP: 26.5		CP: FM 6 bid	CP: 11/596	
Donohue et al.	ICS: 63.0	ICS: 72.5	ICS: 49.6	ICS: 38.3	ICS: 27	3	ICS: SFC 250/50 bid	ICS: 8/701	NR
(2015)	CP: 62.5	CP: 74	CP: 49.3	CP: 37.8	CP: 27.5		CP: UMEC/VI 62.5/ 25 qd	CP: 3/702	
Singh et al.	ICS: 61.4	ICS: 71	ICS: 51.1	ICS: 37.7	NR	3	ICS: SFC 500/50 bid	ICS: 0/358	NR
(2015)	CP: 61.8	CP: 73	CP: 50.2	CP: 37.8			CP: UMEC/VI 62.5/ 25 qd	CP: 1/358	
Zheng et al. (2015)	ICS: 64.4	ICS: 91.3	ICS: 48.4	ICS: 38	NR	5.6	ICS: FF/VI 200/25 qd; FF/VI 100/25 qd; FF/VI 50/25 qd	ICS: 8/480	BMI <25
	CP: 64.7	CP: 90	CP: 48.6	CP: 43.3			CP: P	CP: 4/162	
Zhong et al.	ICS: 65.3	ICS: 89.7	ICS: 52	NR	NR	6	ICS: SFC 500/50 bid	ICS: 10/369	NR
(2015)	CP: 64.8	CP: 91.7	CP: 51.6				CP: IND/GLY 110/50 gd	CP: 3/372	
Beeh et al. (2016)	63.6	64.6	56.4	39.1	NR	1.5	ICS: SFC 50/500 bid; SFC 50/250 bid	ICS: 2/431	NR
							CP: Tio/Olo 5/5 qd; Tio/ Olo 2.5/5 qd	CP: 3/436	
Covelli et al.	ICS: 62.9	ICS: 62	≥30 and ≤70	ICS: 43.2	ICS: 28.4	3	ICS: FF/VI 100/25 gd	ICS: 3/310	NR
(2016)	CP: 62.3	CP: 67	200 and 570	CP: 45.6	CP: 28.6	0	CP: Tio 18 gd	CP: 0/313	
Lee et al. (2016)	ICS: 66.8	ICS: 97.2	ICS: 35.8	NR	ICS: 21.3	3	ICS: BUD/FM 320/9 bid + Tio 18 gd	ICS: 2/289	NR
	CP: 66.9	CP: 94.1	CP: 37		CP: 21.2		CP: Tio 18 gd	CP: 4/289	
Vestbo et al. (2016a)	ICS: 65.0	ICS: 25	ICS: 59.7	ICS: 41	ICS: 28	22	ICS: FF/VI 100/25 qd	ICS: 465/ 8297	NR
	CP: 65.1	CP: 25.5	CP: 59.7	CP: 41	CP: 28		CP: VI 25 qd; P	CP: 377/ 8271	
Vestbo et al. (2016b)	ICS: 67 CP: 67	ICS: 50 CP: 52	NR	NR	ICS: 28 CP: 28	12	ICS: FF/VI 100/25 qd CP: P	ICS: 94/1396 CP: 83/1403	NR
Vogelmeier	ICS: 63.5	ICS: 64.4	ICS: 53.2	ICS: 42.6	NR	6	ICS: SFC 50/500 bid	ICS: 9/466	NR
et al. (2016)	CP: 63.3	CP: 65.7	CP: 53.3	CP: 41.6			CP: ACL/FM 400/12 bid	CP: 3/467	
Wedzicha et al.	ICS: 64.5	ICS: 74.8	ICS: 44.1	NR	NR	12	ICS: SFC 50/500 bid	ICS: 80/1680	NR
(2016)	CP: 64.6	CP: 77.3	CP: 44		100 5	0	CP: IND/GLY 110/50 qd	CP: 53/1678	
	ICS: 68.5	ICS: 77	≤70	ICS: 50.1	ICS: 24.5	6	ICS: FF/VI 100/25 qd	ICS: 2/141	NR

#### **TABLE 1** (*Continued*) Detailed characteristics of the included randomized controlled trials.

Study	Mean Age, y	Male, %	Postbron- chodilator FEV <sub>1</sub> (%	Tobacco use, Pack-years	BMI	Duration, months	Interventions, µg	Pneumonia incidence	Serious pneumonia incidence
			predicted)					Events/ Patients	Events/ Patients
Bhatt et al. (2017)	CP: 68.5	CP: 80.5		CP: 49.4	CP: 24.6		CP: VI 25 qd; P	CP: 3/303	
Ferguson et al. (2017)	ICS: 63.1 CP: 63.9	ICS: 58.6 CP: 56	ICS: 48.5 CP: 48.9	ICS: 39 CP: 40	NR	6	ICS: BUD/FM 320/9 bid CP: FM 9 bid	ICS: 3/605 CP: 6/613	ICS: 0/605 CP: 5/613
Papi et al. (2017)	ICS: 63.4	ICS: 72.6	ICS: 37.9	ICS: 47.4	NR	12	ICS: FP/FM 500/20; FP/ FM 250/10	ICS: 40/1175	NR
	CP: 64	CP: 75.9	CP: 37.7	CP: 50			CP: FM 12 bid	CP: 11/590	
Siler et al.	ICS: 65.3	ICS: 75	ICS: 50.3	ICS: 43.7	NR	3	ICS: FF/VI 100/25 qd	ICS: 7/806	NR
(2017)	CP: 65.4	CP: 77	CP: 50.5	CP: 44.1			CP: VI 25 qd	CP: 7/814	
Vestbo et al. (2017)	ICS: 63	ICS: 75.5	ICS: 36.7	NR	ICS: 26.4	12	ICS: BDP/FM 100/12.5 bid + Tio 18 qd; BDP/ FM 100/6 bid + Tio	ICS:40/1614	ICS: 30/1614
							18 qd		
	CP: 63.3	CP: 77	CP: 36.6		CP: 26.2		CP: Tio 18 qd	CP: 19/1076	CP: 14/1076
Betsuyaku et al.	ICS: 68.6	ICS: 94	ICS: 59.5	ICS: 60.8	NR	6	ICS: SFC 50/250 bid	ICS:6/204	ICS: 4/204
(2018)	CP: 68	CP: 96	CP: 57.8	CP: 54.5			CP: Tio 18 qd	CP: 6/201	CP: 2/201
Chapman et al.	ICS: 65.3	ICS: 69.4	ICS: 57	NR	ICS: 28.2	6	ICS: SFC 50/500 bid	ICS: 9/526	NR
(2018)	CP: 65.5	CP: 71.7	CP: 56.2		CP: 27.8		CP: IND/GLY 110/50 qd	CP: 6/527	
Ferguson et al. (2018a)	ICS: 64.3	ICS: 60.5	ICS: 52.9	ICS: 44.6	ICS: 28.3	6	ICS: BUD/FM 320/10 bid; BUD/FM 160/10 bid; BUD/FM 400/12	ICS: 16/1717	ICS: 12/1717
				CD: 44.0			bid; BUD 320 bid		
Ferguson et al. (2018b)	CP: 64.1 ICS: 65.3	CP: 59.5 ICS: 72.4	CP: 52.6 ICS: 50.3	CP: 44.9 ICS: 45	CP: 28.4 ICS: 26.2	6	CP: FM 10 bid ICS: BGF 320/18/9.6 bid; BFF 320/9.6 bid;	CP: 9/644 ICS: 22/1271	CP: 6/644 NR
							BFF 400/12 bid		
	CP: 65.1	CP: 68.8	CP: 50.2	CP: 45	CP: 26.3		CP: GFF 18/9.6 bid	CP: 10/625	
Frith et al.	ICS: 65.1	ICS: 89.6	ICS: 51.7	ICS: 45.3	ICS: 24.6	3	ICS: SFC 50/500 bid	ICS: 1/250	NR
(2018)	CP: 65	CP: 88.7	CP: 51.3	CP: 44.3	CP: 24.5		CP: IND/GLY 110/50 qd	CP: 1/248	
Lipson et al. (2018)	ICS: 65.3	ICS: 66.6	ICS: 45.6	NR	ICS: 26.6	12	ICS: FF/UMEC/VI 100/ 62.5/25 qd; FF/VI 100/ 25 qd	ICS: 609/ 8285	ICS: 336/ 8285
	CP: 65.2	CP: 66	CP: 45.4		CP: 26.7		CP: UMEC/VI 62.5/ 25 gd	CP: 97/2070	CP: 54/2070
Papi et al. (2018)	ICS: 64.4	ICS: 72	ICS: <50	NR	ICS: 25.7	12	ICS: BDP/FM/GLY 87/ 5/9 bid	ICS: 28/764	ICS: 18/764
, ,	CP: 64.5	CP: 72	CP: <50		CP: 26.6		CP: IND/GLY 85/43 qd	CP: 27/768	CP: 17/768
Huang et al. (2019)	ICS: 63.8	ICS: 87.6	NR	ICS: 33.4	NR	3	ICS: BUD/F 320/9 bid + I/T	ICS: 1/293	NR
	CP: 64.4	CP: 85.3		CP: 32.7			CP: I/T	CP: 0/289	
Ichinose et al. (2019)	ICS: 69.7	ICS: 95.7	ICS: 51.8	ICS: 51.8	ICS: 22.9	6	ICS: BGF 320/18/9.6 bid; BFF 320/9.6 bid; BFF 400/12 bid	ICS: 19/278	NR
	CP: 69	CP: 97.1	CP: 52.2	CP: 52	CP: 22.5		CP: GFF 18/9.6 bid	CP: 5/138	
Kerwin et al. (2019)	ICS: 63.3	ICS: 55	≥25 and <80	ICS: 45.8	ICS: 29	6	ICS: BGF 320/18/9.6 bid; BFF 320/9.6 bid	ICS: 2/282	ICS: 2/282
	CP: 62.4	CP: 50		CP: 50	CP: 29		CP: GFF 18/9.6 bid	CP: 4/174	CP: 4/174
Rabe et al. (2020)	ICS: 64.6	ICS: 60.1	ICS: 43.4	ICS: 47.3	NR	12	ICS: BGF 320/18/9.6 bid; BGF 160/18/9.6 bid; BFF 320/9.6 bid	ICS: 261/ 6404	NR
							S.G, DIT 020/0.0 DIU		

RCT, randomized controlled trial; FEV<sub>1</sub>, forced expiratory volume in the first second; BMI, body-mass index; ICSs, inhaled corticosteroids; CP, control or placebo; BUD, budesonide; NR, not reported; bid, twice daily; qd, once daily; FP, fluticasone propionate; S, salmeterol; SFC, fluticasone propionate/salmeterol; EOC, eosinophil counts; BUD/FM, budesonide/formoterol fumarate; FM, formoterol fumarate; MF, mometasone furoate; Tio, tiotropium/olodaterol; BDP, Beclomethasone dipropionate; FF/VI, fluticasone furoate/vilanterol; VI, vilanterol; VI, vilanterol; UMEC/VI, umeclidinium/vilanterol; ACL/FM, aclidinium/formoterol; IND/GLY, indacaterol/glycopyrronium; FF/UMEC/VI, fluticasone furoate/linium/vilanterol; BDP/FM/GLY, beclomethasone/formoterol; BFF, budesonide/formoterol; GFF, glycopyrroniate/formoterol.

et al., 2000; Calverley et al., 2003; Szafranski et al., 2003; Aaron et al., 2007; Calverley et al., 2007; Kardos et al., 2007; Calverley et al., 2008; Ferguson et al., 2008; Tashkin et al., 2008;

Wedzicha et al., 2008; Anzueto et al., 2009; Rennard et al., 2009; Welte et al., 2009; Calverley et al., 2010; Dransfield et al., 2011; Doherty et al., 2012; Hanania et al., 2012; Jung et al.,



2012; Sharafkhaneh et al., 2012; Tashkin et al., 2012a, Tashkin et al. 2012b; Dransfield et al., 2013; Fukuchi et al., 2013; Kerwin et al., 2013; Martinez et al., 2013; Vogelmeier et al., 2013; Magnussen et al., 2014; Ohar et al., 2014; Pepin et al., 2014; Rossi et al., 2014; Wedzicha et al., 2014; Donohue et al., 2015; Singh et al., 2015; Zheng et al., 2015; Zhong et al., 2015; Beeh et al., 2016; Covelli et al., 2016; Lee et al., 2016; Vestbo et al., 2016a; Vestbo et al., 2016b; Vogelmeier et al., 2016; Wedzicha et al., 2016; Bhatt et al., 2017; Ferguson et al., 2017; Papi et al., 2017; Siler et al., 2017; Vestbo et al., 2017; Betsuyaku et al., 2018; Chapman et al., 2018; Ferguson et al., 2018a; Ferguson et al., 2018b; Frith et al., 2018; Lipson et al., 2018; Papi et al., 2018; Huang et al., 2019; Ichinose et al., 2019; Kerwin et al., 2019; Rabe et al., 2020). These trials enrolled 103,477 patients. of whom 60,733 received ICSs treatment and 42,744 received non-ICSs treatment. The flowchart is shown in Figure 1. The studies included were published between 1999 and 2020, with sample size raging from 249 to 16,568 patients. All studies provided data on pneumonia, 14 of which provided data on serious pneumonia. Among the studies, 35 RCTs (67,109 patients) compared fluticasone and control, 17 RCTs (25,071 patients) compared budesonide and control, four RCTs (5,413 patients) compared mometasone and control, and four RCTs (5,884 patients) compared beclomethasone and control, respectively. No RCTs investigated triamcinolone or ciclesonide and the pneumonia risk in COPD patients. The detailed characteristics of the included RCTs are summarized in Table 1.

## Assessment of Risk of Bias

All included studies were assessed using the Cochrane Collaboration risk of bias assessment tool. The results are presented in **Figures 2**, **3**. Thirty-five RCTs were assessed as being at low risk of bias for all aspects. Four had a high risk of bias for performance bias (blinding of participants and personnel) and detection bias (Blinding of outcome assessment). Twenty-two had an unclear risk for random sequence generation, selective reporting, allocation concealment, or other bias (**Figures 2**, **3**).

## Various Types of ICSs and Pneumonia Risk

Compared with non-ICSs treatment, ICSs treatment significantly increased the pneumonia risk (Peto OR, 1.43; 95% CI, 1.34–1.53). Subgroup analysis based on types of ICSs showed that all types of ICSs increased the pneumonia risk ([fluticasone: Peto OR, 1.47; 95% CI, 1.36–1.59]; [budesonide: Peto OR, 1.24; 95% CI, 1.05–1.47]; [mometasone: Peto OR, 1.62; 95% CI, 1.03–2.49]; [beclomethasone: Peto OR, 1.43; 95% CI, 1.03–1.97]). Test for subgroup differences (I<sup>2</sup> = 16.4%) indicated that there was no significant difference in the pneumonia risk associated with different types of ICSs (**Table 2** and **Figure 4**).

# Different Doses of ICSs and Pneumonia Risk

Of the included trials, 23 RCTs (54,287 patients), 26 RCTs (27,302 patients), and 27 RCTs (32,592 patients) assessed high-dose, medium-dose, and low-dose ICSs and pneumonia risk, respectively. Subgroup analysis showed that there was a dose-response relationship between ICSs treatment and pneumonia risk. Low-dose (Peto OR, 1.33; 95% CI, 1.22–1.45), medium-dose (Peto OR, 1.50; 95% CI, 1.28–1.76), and high-dose (Peto OR, 1.64; 95% CI, 1.45–1.85) ICSs all significantly increased the pneumonia risk. Test for subgroup differences (I<sup>2</sup> = 74%) indicated that there was a significant difference in the pneumonia risk associated with different doses of ICSs (**Table 2** and **Figure 5**).

# Different Treatment Durations of ICSs and Pneumonia Risk

Of the included trials, 31 RCTs (26,408 patients), and 28 RCTs (76,826 patients) assessed short-term ICSs treatment and long-term ICSs treatment and pneumonia risk. Subgroup analysis showed that both short-term ICSs treatment (Peto OR, 1.30; 95% CI, 1.04–1.63) and long-term ICSs treatment (Peto OR, 1.44; 95% CI, 1.34–1.55) significantly increased the pneumonia risk. Test for subgroup differences ( $I^2 = 0\%$ ) indicated that there was no significant difference in the pneumonia risk associated with different treatment durations of ICSs (**Table 2** and **Figure 6**).



# ICSs Associated Pneumonia in COPD Patients With Different Severity

Eighteen RCTs (30,809 patients), 34 RCTs (65,773 patients) and two RCTs (1,148 patients) assessed ICSs associated pneumonia in moderate, severe, and very severe COPD patients, respectively. Subgroup analysis showed that the pneumonia risk was related with COPD severity. ICSs treatment significantly increased the pneumonia risk in all severity subgroups of COPD patients: ([Moderate COPD: Peto OR, 1.26; 95% CI, 1.11–1.43]; [Severe COPD: Peto OR, 1.54; 95% CI, 1.42–1.68]; [Very severe COPD: Peto OR, 2.52; 95% CI, 1.88–3.38]) (**Table 2** and **Figure 7**). Test for subgroup differences ( $I^2 = 90.1\%$ ) indicated that there was a significant difference in the pneumonia risk in patients with different severity.

# ICSs Associated Pneumonia in COPD Patients With Different Age

Thirty-five RCTs (50,802 patients) and 19 RCTs (46,963 patients) assessed ICSs associated pneumonia in patients with different age. Subgroup analysis showed that ICSs treatment significantly increased the pneumonia risk in patients both age subgroups: ([<65 yr old: Peto OR, 1.43; 95% CI, 1.28–1.60]; [≥65 yr old: Peto OR, 1.41; 95% CI, 1.29–1.54]). Test for subgroup differences (I<sup>2</sup> = 0%) indicated that there was no significant difference in the pneumonia risk in patients with different age (**Table 2** and **Figure 8**).

# ICSs Associated Pneumonia in COPD Patients With Different BMI

Eight RCTs (4,443 patients) and 23 RCTs (54,867 patients) assessed ICSs associated pneumonia in patients with different BMI. Subgroup analysis showed that ICSs treatment significantly increased the pneumonia risk in patients both BMI subgroups: ([<25: Peto OR, 1.47; 95% CI, 1.02–2.12]; [ $\geq$ 25: Peto OR, 1.43; 95% CI, 1.31–1.55]). Test for subgroup differences (I<sup>2</sup> = 0%) indicated that there was no significant difference in the pneumonia risk in patients with different BMI (**Table 2** and **Figure 9**).

# Various Types of ICSs and Serious Pneumonia Risk

Of the included trials, 15 RCTs (29,008 patients) offered data on serious pneumonia associated with ICSs treatment. Compared with non-ICSs treatment, ICSs treatment significantly increased the serious pneumonia risk (Peto OR, 1.55; 95% CI, 1.31–1.84). Of the included RCTs, seven RCTs (17,091 patients) assessed fluticasone and serious pneumonia risk, six RCTs (7,695 patients) assessed budesonide and two RCTs (4,222 patients) assessed beclomethasone, respectively. Subgroup analysis showed that only fluticasone significantly increased the serious pneumonia

### **TABLE 2** | Summary of the pooled results.

Pooled results	No. of Patients	No. of Studies	Peto OR (95% CI)	Test for subgroup differences
Various types of ICSs and pneumonia risk				l <sup>2</sup> = 16.4%
All types of ICSs	103,477	59	1.43 (1.34–1.53)	
Fluticasone	67,109	35	1.47 (1.36-1.59)	
Budesonide	25,071	17	1.24 (1.05-1.47)	
Mometasone furoate	5,413	4	1.62 (1.05-2.49)	
Beclomethasone dipropionate	5,884	4	1.43 (1.03-1.97)	
Different doses of ICSs and pneumonia risk			, , , , , , , , , , , , , , , , , , ,	$l^2 = 74\%$
_ow -dose	54,287	23	1.33 (1.22-1.45)	
Medium-dose	27,302	26	1.50 (1.28–1.76)	
High-dose	32,592	27	1.64 (1.45–1.85)	
Different treatment durations of ICSs and pneumonia risk			· · · · · · · · · · · · · · · · · · ·	$l^2 = 0\%$
≤6 mo	26,408	31	1.30 (1.04–1.63)	
>6 mo	76,826	28	1.44 (1.34–1.55)	
CSs associated pneumonia in COPD patients with different severity	,			$ ^2 = 90.1\%$
Noderate COPD (GOLD stage II)	30,809	18	1.26 (1.11–1.43)	
Severe COPD (GOLD stage III)	65,773	34	1.54 (1.42-1.68)	
/ery severe COPD (GOLD stage IV)	1148	2	2.52 (1.88-3.38)	
CSs associated pneumonia in COPD patients with different age			- (,	$l^2 = 0\%$
:65 yr	50,802	35	1.43 (1.28-1.60)	
265 yr	46,963	19	1.41 (1.29–1.54)	
CSs associated pneumonia in COPD patients with different BMI	,			$l^2 = 0\%$
×25	4,443	8	1.47 (1.02-2.12)	
	54,867	23	1.43 (1.31–1.55)	
/arious types of ICSs and serious pneumonia risk	0 1,001	20		$l^2 = 61.9\%$
All types of ICSs	29,008	15	1.55 (1.31–1.84)	
Fluticasone	17,091	7	1.75 (1.44–2.14)	
Budesonide	7,695	6	1.06 (0.68–1.65)	
Beclomethasone dipropionate	4,222	2	1.24 (0.79–1.95)	
Sensitivity analysis after excluding RCTs with high risk of bias (various types of ICSs and	.,	-		$l^2 = 23.2\%$
pneumonia risk)				. 20.270
All types of ICSs	99,063	55	1.45 (1.35–1.56)	
Fluticasone	63,855	33	1.50 (1.38–1.62)	
Budesonide	23,911	15	1.25 (1.06–1.48)	
Vometasone furoate	5,413	4	1.62 (1.05–2.49)	
Beclomethasone dipropionate	5,884	4	1.43 (1.03–1.97)	

ICSs, inhaled corticosteroids; Peto OR, Peto odds ratio; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive; BMI, body mass index.

risk (Peto OR, 1.75; 95% CI, 1.44–2.14) while budesonide (Peto OR, 1.06; 95% CI, 0.68–1.65) and beclomethasone (Peto OR, 1.24; 95% CI, 0.79–1.95) did not. Test for subgroup differences ( $I^2 = 61.9\%$ ) indicated that there was a significant difference in the serious pneumonia risk associated with different types of ICSs (**Table 2** and **Figure 10**).

## **Sensitivity Analysis**

After excluding four RCTs (4,414 patients) with high risk of bias, the pooled results were similar in magnitude and direction to those (pooled results of association between various types of ICSs and pneumonia risk) obtained from all included RCTs (**Table 2**).

# DISCUSSION

In this meta-analysis of 59 RCTs (including 103,477 patients), all types of ICSs, not only fluticasone, increased the pneumonia

risk in COPD patients in a dose-dependent manner, and the risk was particularly evident in more severe COPD patients. Moreover, fluticasone increased the risk of serious pneumonia, while budesonide and beclomethasone did not. To our knowledge, this study was the first meta-analysis which revealed the pneumonia risk associated ICSs treatment was related with COPD severity. In addition, there was a doseresponse relationship between the pneumonia risk and ICSs treatment.

At present, ICSs are widely used in the maintenance treatment of COPD patients. Since numerous COPD patients use ICSs every day, both its efficacy and safety should be considered. Although some studies have reported that fluticasone increases the pneumonia risk in COPD patients, whether other types of ICSs would increase the pneumonia risk in COPD patients remains controversial (Sin et al., 2009; Singh et al., 2009; Kew and Seniukovich, 2014; Festic et al., 2016; Yang et al., 2019; Zhang et al., 2020). In addition, it is still unclear whether different medication details and baseline characteristics (severity, age, and

Study or Subgroup	ICSs Events Tota	Contr Events		Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% Cl
Fluticasone Burge 2000	20 376	9	375	0.8%	2.19 [1.04, 4.61]	<u> </u>
Aaron 2007	1 14	1	304	0.1%	2.25 [0.12, 43.76]	
Calverley 2007	217 3098		3086	9.8%	1.77 [1.43, 2.21]	-
Kardos 2007	23 50		487	0.9%	2.88 [1.39, 5.96]	
Ferguson 2008 Wedzicha 2008	29 394 50 658		388 665	1.3% 2.1%	1.93 [1.05, 3.54] 2.13 [1.33, 3.40]	
Anzueto 2009	26 394		403	1.0%	2.59 [1.33, 5.06]	
Dransfield 2011	3 123		126	0.1%	7.70 [0.79, 74.69]	
Hanania 2012	2 173		169	0.1%	7.26 [0.45, 116.60]	
Jung 2012	2 223		232	0.1%	1.04 [0.15, 7.44]	
Dransfield 2013	154 243		818	3.9%	1.78 [1.26, 2.51]	
Kerwin 2013 Martinez 2013	12 618 10 816		412 408	0.6% 0.3%	1.00 [0.41, 2.47] 2.13 [0.64, 7.12]	
Vogelmeier 2013	4 264		258	0.3%	7.31 [1.02, 52.17]	
Magnussen 2014	72 1243		1242	4.0%	1.06 [0.75, 1.49]	+
Ohar 2014	13 314		325	0.7%	1.36 [0.59, 3.12]	
Pepin 2014	3 12	0	130	0.1%	7.69 [0.79, 74.57]	
Rossi 2014	2 288		293	0.1%	7.54 [0.47, 120.92]	
Donohue 2015	8 70	3	702	0.3%	2.50 [0.76, 8.19]	·
Singh 2015 Zheng 2015	0 358		358 162	0.0% 0.3%	0.14 [0.00, 6.82] 0.65 [0.17, 2.40]	·
Zhong 2015	10 369		372	0.3%	3.01 [1.01, 9.02]	
Beeh 2016	2 43		436	0.2%	0.68 [0.12, 3.92]	
Covelli 2016	3 310		313	0.1%	7.51 [0.78, 72.46]	
Vestbo 2016 (1)	465 829	377	8271	24.2%	1.24 [1.08, 1.43]	-
Vestbo 2016 (2)	94 1396		1403	5.0%	1.15 [0.85, 1.56]	+-
Vogelmeier 2016	9 466		467	0.4%	2.76 [0.88, 8.61]	
Wedzicha 2016	80 1680		1678	3.9%	1.52 [1.08, 2.16]	
Bhatt 2017	2 14		303	0.1%	1.47 [0.22, 9.73]	
Papi 2017 Siler 2017	40 1175 7 806		590 814	1.3% 0.4%	1.73 [0.96, 3.12]	
Betsuyaku 2018	6 204		201	0.4%	1.01 [0.35, 2.89] 0.98 [0.31, 3.10]	
Chapman 2018	9 526		527	0.4%	1.50 [0.54, 4.16]	
Frith 2018	1 250		248	0.1%	0.99 [0.06, 15.90]	
Lipson 2018	609 828		2070	12.8%	1.52 [1.26, 1.84]	
Subtotal (95% CI)	38073		29036	76.2%	1.47 [1.36, 1.59]	•
Total events	1996	968				
Heterogeneity: Chi <sup>2</sup> = 4 Test for overall effect: Z			%			
Budesonide						
Vestbo 1999	16 14	24	145	1.0%	0.63 [0.32, 1.23]	
Calverley 2003	13 51		511	0.7%	1.45 [0.62, 3.37]	
Szafranski 2003	6 208	9	205	0.4%	0.65 [0.23, 1.82]	
Tashkin 2008	17 1120		584	0.6%	1.45 [0.61, 3.44]	- <del>-</del> -
Rennard 2009	30 988		976	2.0%	0.73 [0.46, 1.18]	
Welte 2009	3 33		329	0.2%	0.99 [0.20, 4.95]	
Calverley 2010	7 238		233	0.2%	4.49 [1.11, 18.13]	
Sharafkhaneh 2012	45 815		403	1.4%	1.89 [1.07, 3.34]	
Fukuchi 2013	8 636		657	0.4%	1.18 [0.43, 3.27]	
Lee 2016	2 289		289 613	0.2% 0.3%	0.51 [0.10, 2.55]	
Ferguson 2017 Ferguson 2018 (1)	16 171		644	0.6%	0.52 [0.14, 1.92] 0.64 [0.26, 1.55]	
Ferguson 2018 (2)	22 127		625	0.8%	1.08 [0.51, 2.28]	
Huang 2019	1 293		289	0.0%	7.29 [0.14, 367.37]	
Ichinose 2019	19 278		138	0.6%	1.80 [0.75, 4.32]	+
Kerwin 2019	6 283		174	0.4%	0.44 [0.15, 1.30]	
Rabe 2020	261 6404	48	2125	6.8%	1.68 [1.29, 2.19]	<u> </u>
Subtotal (95% CI)	16131	100000	8940	16.8%	1.24 [1.05, 1.47]	•
Total events	475	200				
Heterogeneity: Chi <sup>2</sup> = 3 Test for overall effect: Z		.01); l <sup>2</sup> = 49	%			
Mometasone furoate						
Calverley 2008	25 616	6	295	0.8%	1.85 [0.86, 3.98]	+
Doherty 2012	16 713	6	479	0.6%	1.72 [0.73, 4.06]	+
Tashkin 2012 (1)	19 135	9	900	0.8%	1.39 [0.65, 2.98]	
Tashkin 2012 (2)	7 634		421	0.3%	1.52 [0.43, 5.41]	
Subtotal (95% CI)	3318		2095	2.5%	1.62 [1.05, 2.49]	◆
Total events	67	24			-	
Heterogeneity: Chi <sup>2</sup> = 0. Test for overall effect: Z	30, df = 3 (P = 0.96					
Beclomethasone dipro						
Calverley 2010	5 232		233	0.2%	3.87 [0.77, 19.32]	+
Wedzicha 2014	23 601		596	1.0%	2.05 [1.04, 4.05]	<b>—</b> —
Vestbo 2017	40 1614		1076	1.7%	1.39 [0.82, 2.36]	+
Papi 2018	28 764	27	768	1.6%	1.04 [0.61, 1.79]	-t_
Subtotal (95% CI)	3211		2673	4.5%	1.43 [1.03, 1.97]	
Total events Heterogeneity: Chi <sup>2</sup> = 3.		58 ); I² = 22%				
Test for overall effect: Z	= 2.16 (P = 0.03)					
Total (95% CI)	60733		42744	100.0%	1.43 [1.34, 1.53]	•
Total events	2634	1250	0/.			· · · · · ·
Heterogeneity: Chi <sup>2</sup> = 86			70			0.01 0.1 1 10 10
Test for overall effect: Z			0 31) 12	= 16.4%		Favours ICSs Favours Control
Test for subaroup different						

		1084	~	ntrol		Peto Odds Ratio	Peto Odds Ratio
	Study or Subgroup	ICSs Events T		ontrol ts Tota	Weight		Peto Odds Ratio Peto, Fixed. 95% Cl
	Low-dose				-		
	Szafranski 2003 Tashkin 2008		208 281	9 205 6 584			
	Rennard 2009			6 584 10 976			
	Calverley 2010		232	1 233		3.87 [0.77, 19.32]	
	Sharafkhaneh 2012			11 403		1.72 [0.83, 3.56]	
	Dransfield 2013 Fukuchi 2013		626 636	27 818 7 657		1.77 [1.21, 2.59] 1.18 [0.43, 3.27]	
	Kerwin 2013		618	8 412			
	Martinez 2013	3	408	2 408	0.3%	1.49 [0.26, 8.67]	
	Pepin 2014		127	0 130			
	Wedzicha 2014 Zheng 2015		601 321	11 596 4 162			
	Covelli 2016		310	0 313			· · · · · · · · · · · · · · · · · · ·
	Vestbo 2016 (1)			77 8271			•
	Vestbo 2016 (2)			33 1403		1.15 [0.85, 1.56]	
	Bhatt 2017 Siler 2017		141 806	3 303 7 814			
	Vestbo 2017			19 1076			+
	Ferguson 2018 (1)	7	637	9 644	0.8%	0.79 [0.29, 2.10]	
	Lipson 2018			97 2070			*
	Papi 2018 Huang 2019		764 293	27 768 0 289			<b>,</b>
	Rabe 2020			48 2125			-
	Subtotal (95% CI)		627	23660			•
	Total events	1533	7				
	Heterogeneity: Chi <sup>2</sup> = 27. Test for overall effect: Z =			= 21%			
	rest for overall effect. 2 -	0.20 (F < 0.0	5001)				
	Medium-dose	11-21					
	Calverley 2003 Aaron 2007		254 145	9 511 1 304			
	Aaron 2007 Ferguson 2008			1 304 15 388			
	Tashkin 2008		839	6 584			
	Anzueto 2009	26	394	10 403	5.7%	2.59 [1.33, 5.06]	
	Rennard 2009		494 331	10 976			
	Welte 2009 Dransfield 2011		123	3 329 0 126			
	Doherty 2012		239	6 479			
	Hanania 2012		173	0 169		7.26 [0.45, 116.60]	
	Jung 2012 Sharafkhaneh 2012		223 407	2 232 11 403			
	Tashkin 2012 (1)		407	9 900		2.31 [1.20, 4.47] 1.12 [0.37, 3.44]	
	Tashkin 2012 (2)		207	3 421		0.70 [0.09, 5.63]	
	Ohar 2014			10 325		1.36 [0.59, 3.12]	
	Donohue 2015		701 211	3 702 3 436		2.50 [0.76, 8.19]	
	Beeh 2016 Lee 2016		289	4 289			
	Ferguson 2017	3	605	6 613	1.5%	0.52 [0.14, 1.92]	
	Papi 2017			11 590		2.07 [1.05, 4.10]	
	Betsuyaku 2018 Ferguson 2018 (1)		204 861	6 201 9 644			
	Ferguson 2018 (2)			9 644 10 625			
	Ichinose 2019		278	5 138			
	Kerwin 2019		282	8 174			
	Rabe 2020 Subtotal (95% CI)		260 215	48 2125 13087			
	Total events	425		38	100.0%	1.50 [1.20, 1.70]	•
	Heterogeneity: Chi <sup>2</sup> = 34.						
	Test for overall effect: Z =						
	High-dose						
	Vestbo 1999	16	145	24 145	3.3%	0.63 [0.32, 1.23]	
	Calverley 2003	5	257	9 511	1.2%	1.11 [0.36, 3.40]	
	Burge 2000		376	9 375			
	Calverley 2007 Kardos 2007			24 3086 7 487			
	Calverley 2008		616	6 295		1.85 [0.86, 3.98]	
	Wedzicha 2008	50	658	24 665	6.8%	2.13 [1.33, 3.40]	
	Calverley 2010		238	1 233			
	Doherty 2012 Tashkin 2012 (1)		478 905	6 479 9 900			
	Tashkin 2012 (1) Tashkin 2012 (2)		905 427	3 421	0.00/		
	Dransfield 2013			27 818			
	Martinez 2013	7	408	2 408	0.9%	3.07 [0.83, 11.42]	
	Vogelmeier 2013 Magnussen 2014		264	0 258		7.31 [1.02, 52.17] 1.06 [0.75, 1.49]	-
	Magnussen 2014 Rossi 2014		243 288	58 1242 0 293			
	Singh 2015	0	358	1 358	0.1%	0.14 [0.00, 6.82]	
	Zheng 2015	5	160	4 162	2 0.8%	1.27 [0.34, 4.78]	<u> </u>
	Zhong 2015		369	3 372		3.01 [1.01, 9.02]	
	Beeh 2016 Vogelmeier 2016		217 466	3 436 3 467		0.69 [0.09, 5.54] 2.76 [0.88, 8.61]	<u> </u>
	Wedzicha 2016			53 1678		1.52 [1.08, 2.16]	-
	Papi 2017	17	587	11 590	2.6%	1.56 [0.74, 3.30]	
	Chapman 2018		526	6 527			
	Ferguson 2018 (1) Ferguson 2018 (2)		219 318	9 644 10 625		0.98 [0.26, 3.63] 0.79 [0.26, 2.42]	
	Frith 2018		250	1 248			
	Subtotal (95% CI)	15	369	16723			•
	Total events	674	4				
	Heterogeneity: Chi <sup>2</sup> = 33.			= 23%			
	Test for overall effect: Z =	· 1.95 (P < 0.0	5001)				
						0.01	
	Testforest	0.12 -	10 41 5	- 0 - 0	19 - 71 0		0.1 1 10 100 Favours ICSs Favours Control
	Test for subaroup differen	ices: Chi <sup>2</sup> = 7.	ru. df = 2 (	- = 0.02).	ı² = 74.0%	b	
FIGURE 5   Different doses of in	holod cortionator-	to and -	0	in rial.			

o	ICSs		Contr			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
≪ 6 months			-				
Tashkin 2008		1120	6	584	6.7%	1.45 [0.61, 3.44]	
Welte 2009	3	331	3	329	1.9%	0.99 [0.20, 4.95]	
Dransfield 2011	3	123	0	126	1.0%	7.70 [0.79, 74.69]	
Hanania 2012	2	173	0	169	0.6%	7.26 [0.45, 116.60]	. ,
Jung 2012	2	223	2	232	1.3%	1.04 [0.15, 7.44]	
Fukuchi 2013	8	636	7	657	4.8%	1.18 [0.43, 3.27]	
Kerwin 2013	12 10	618 816	8 2	412 408	6.1%	1.00 [0.41, 2.47]	
Martinez 2013 Vogelmeier 2013	4	264	2	258	3.4% 1.3%	2.13 [0.64, 7.12]	
Ohar 2014	13	204 314	10	325	7.2%	7.31 [1.02, 52.17] 1.36 [0.59, 3.12]	_ <b>_</b>
Pepin 2014	3	127	0	130	1.0%	7.69 [0.79, 74.57]	· · · · · · · · · · · · · · · · · · ·
Rossi 2014	2	288	0	293	0.7%	7.54 [0.47, 120.92]	<b>,</b>
Donohue 2015	8	701	3	702	3.6%	2.50 [0.76, 8.19]	
Singh 2015	0	358	1	358	0.3%	0.14 [0.00, 6.82]	
Zheng 2015	8	480	4	162	2.9%	0.65 [0.17, 2.40]	
Zhong 2015	10	369	3	372	4.2%	3.01 [1.01, 9.02]	
Beeh 2016	2	431	3	436	1.6%	0.68 [0.12, 3.92]	
Covelli 2016	3	310	0	313	1.0%	7.51 [0.78, 72.46]	+
Lee 2016	2	289	4	289	1.9%	0.51 [0.10, 2.55]	
Vogelmeier 2016	9	466	3	467	3.9%	2.76 [0.88, 8.61]	<u>↓</u>
Bhatt 2017	2	141	3	303	1.4%	1.47 [0.22, 9.73]	
Ferguson 2017	3	605	6	613	2.9%	0.52 [0.14, 1.92]	— <del>•</del>
Siler 2017	7	806	7	814	4.5%	1.01 [0.35, 2.89]	
Betsuyaku 2018	6	204	6	201	3.8%	0.98 [0.31, 3.10]	
Chapman 2018	9	526	6	527	4.8%	1.50 [0.54, 4.16]	- <del></del>
Ferguson 2018 (1)	16	1717	9	644	6.4%	0.64 [0.26, 1.55]	
Ferguson 2018 (2)	22	1271	10	625	9.1%	1.08 [0.51, 2.28]	- <del>-</del>
Frith 2018	1	250	1	248	0.6%	0.99 [0.06, 15.90]	
Huang 2019	1	293	0	289	0.3%	7.29 [0.14, 367.37]	· · · ·
Ichinose 2019	19	278	5	138	6.5%	1.80 [0.75, 4.32]	
Kerwin 2019	6	282	8	174	4.2%	0.44 [0.15, 1.30]	
Subtotal (95% CI)		4810		11598	100.0%	1.30 [1.04, 1.63]	•
Total events Heterogeneity: Chi <sup>2</sup> = 33.7	213		120				
Test for overall effect: Z = > 6 months							
Vestbo 1999	16	145	24	145	1.2%	0.63 [0.32, 1.23]	
Calverley 2003	13	511	9	511	0.7%	1.45 [0.62, 3.37]	
Burge 2000	20	376	9	375	0.9%	2.19 [1.04, 4.61]	
Szafranski 2003	6	208	9	205	0.5%	0.65 [0.23, 1.82]	
Aaron 2007 Calverley 2007	1 217	145 3098	1 124	304 3086	0.1% 10.8%	2.25 [0.12, 43.76]	-
Calverley 2007 Kardos 2007	217	3098 507	124	3086 487	1.0%	1.77 [1.43, 2.21] 2.88 [1.39, 5.96]	
Calverley 2008	25	616	6	295	0.9%	1.85 [0.86, 3.98]	<b>↓</b>
Ferguson 2008	29	394	15	388	1.4%	1.93 [1.05, 3.54]	<u> </u>
Wedzicha 2008	29 50	658	24	665	2.3%	2.13 [1.33, 3.40]	
Anzueto 2009	26	394	10	403	1.2%	2.59 [1.33, 5.06]	<del></del>
Rennard 2009	30	988	40	976	2.3%	0.73 [0.46, 1.18]	+
Calverley 2010	12	460	1	233	0.4%	3.26 [1.02, 10.41]	
Doherty 2012	16	717	6	479	0.7%	1.72 [0.73, 4.06]	+
Sharafkhaneh 2012	45	815	11	403	1.6%	1.89 [1.07, 3.34]	
Tashkin 2012 (1)		1351	9	900	0.9%	1.39 [0.65, 2.98]	- <del> </del>
Tashkin 2012 (2)	7	634	3	421	0.3%	1.52 [0.43, 5.41]	
Dransfield 2013		2437	27	818	4.3%	1.78 [1.26, 2.51]	<del>~</del>
Magnussen 2014		1243	68	1242	4.4%	1.06 [0.75, 1.49]	+
Wedzicha 2014	23	601	11	596	1.1%	2.05 [1.04, 4.05]	<u> </u>
Vestbo 2016 (1)		8297	377	8271	26.7%	1.24 [1.08, 1.43]	-
		1396	83	1403	5.5%	1.15 [0.85, 1.56]	+-
Vestbo 2016 (2)		1680	53	1678	4.3%	1.52 [1.08, 2.16]	<del>~</del> -
		1175	11	590	1.5%	1.73 [0.96, 3.12]	<u>├</u>
Vestbo 2016 (2) Wedzicha 2016			19	1076	1.9%	1.39 [0.82, 2.36]	+
Vestbo 2016 (2) Wedzicha 2016 Papi 2017	40	1614		2070	14.1%	1.52 [1.26, 1.84]	+
Vestbo 2016 (2) Wedzicha 2016 Papi 2017 Vestbo 2017	40 40	1614 8285	97				
Vestbo 2016 (2) Wedzicha 2016 Papi 2017 Vestbo 2017 Lipson 2018	40 40 609	8285			1.8%	1.04 [0.61. 1.79]	
Vestbo 2016 (2) Wedzicha 2016 Papi 2017 Vestbo 2017 Lipson 2018 Papi 2018	40 40 609 28	8285 764	27	768	1.8% 7.5%	1.04 [0.61, 1.79] 1.68 [1.29, 2.19]	T
Vestbo 2016 (2) Wedzicha 2016 Papi 2017 Vestbo 2017 Lipson 2018	40 40 609 28 261	8285	27 48	768 2125	1.8% 7.5% <b>100.0%</b>	1.04 [0.61, 1.79] 1.68 [1.29, 2.19] 1.44 [1.34, 1.55]	T.
Vestbo 2016 (2) Wedzicha 2016 Papi 2017 Vestbo 2017 Lipson 2018 Papi 2018 Rabe 2020	40 40 609 28 261	8285 764 6404	27 48	768 2125	7.5%	1.68 [1.29, 2.19]	Ŧ
Vestbo 2016 (2) Wedzicha 2016 Papi 2017 Vestbo 2017 Lipson 2018 Papi 2018 Rabe 2020 Subtotal (95% CI)	40 40 609 28 261 4 2421	8285 764 6404 15913	27 48 1129	768 2125 <b>30913</b>	7.5%	1.68 [1.29, 2.19]	Ŧ
Vestbo 2016 (2) Wedzicha 2016 Papi 2017 Lipson 2017 Lipson 2018 Papi 2018 Rabe 2020 Subtotal (95% CI) Total events	40 40 609 28 261 4 2421 62, df = 27 (f	8285 764 6404 <b>I5913</b> P = 0.0	27 48 1129 05); I <sup>2</sup> = 4	768 2125 <b>30913</b>	7.5%	1.68 [1.29, 2.19]	Ť
Vestbo 2016 (2) Wedzicha 2016 Papi 2017 Lipson 2018 Papi 2018 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 49.6	40 40 609 28 261 4 2421 62, df = 27 (f	8285 764 6404 <b>I5913</b> P = 0.0	27 48 1129 05); I <sup>2</sup> = 4	768 2125 <b>30913</b>	7.5%	1.68 [1.29, 2.19] 1.44 [1.34, 1.55]	
Vestbo 2016 (2) Wedzicha 2016 Papi 2017 Lipson 2018 Papi 2018 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 49.6	40 40 609 28 261 4 2421 62, df = 27 (f 10.00 (P < f	8285 764 6404 <b>I5913</b> P = 0.0 0.0000	27 48 1129 05); I <sup>2</sup> = 4 1)	768 2125 <b>30913</b>	7.5% 100.0%	1.68 [1.29, 2.19]	1 0.1 1 10 100 Favours ICSs Favours Control

	ICSs		trol		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup		I Event	s Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
Moderate COPD (GOLD	stage II)					
Vestbo 1999	16 14	5 24	145	3.4%	0.63 [0.32, 1.23]	+
Burge 2000	20 37	6 9	375	2.8%	2.19 [1.04, 4.61]	
Welte 2009	3 12			0.3%	7.70 [0.79, 74.69]	+
Hanania 2012	2 17	3 (	169	0.2%	7.26 [0.45, 116.60]	
Vogelmeier 2013	4 26			0.4%	7.31 [1.02, 52.17]	· · · · · · · · · · · · · · · · · · ·
Rossi 2014	2 28			0.2%	7.54 [0.47, 120.92]	<b>,</b>
Singh 2015	0 35			0.1%	0.14 [0.00, 6.82]	· · · · · · · · · · · · · · · · · · ·
Zhong 2015	10 36			1.3%	3.01 [1.01, 9.02]	
Beeh 2016	2 43			0.5%	0.68 [0.12, 3.92]	· · · · · · · · · · · · · · · · · · ·
Vestbo 2016 (1)	465 829			78.9%	1.24 [1.08, 1.43]	
Vogelmeier 2016	405 829 9 46			1.2%	2.76 [0.88, 8.61]	
Siler 2017	7 80			1.2%		
	6 20			1.4%	1.01 [0.35, 2.89]	
Betsuyaku 2018					0.98 [0.31, 3.10]	
Chapman 2018	9 52			1.5%	1.50 [0.54, 4.16]	
Ferguson 2018 (1)	16 171			1.9%	0.64 [0.26, 1.55]	
Ferguson 2018 (2)	22 127			2.7%	1.08 [0.51, 2.28]	
Frith 2018	1 25			0.2%	0.99 [0.06, 15.90]	
Ichinose 2019	19 27			2.0%	1.80 [0.75, 4.32]	
Subtotal (95% CI)	1634		14467	100.0%	1.26 [1.11, 1.43]	▼
Total events	613	464				
Heterogeneity: Chi <sup>2</sup> = 24.			31%			
Test for overall effect: Z =	3.69 (P = 0.000	2)				
Severe COPD (GOLD st	• /					
Calverley 2003	13 51	1 9	511	1.0%	1.45 [0.62, 3.37]	- <del> -</del>
Szafranski 2003	6 20	в 9	205	0.7%	0.65 [0.23, 1.82]	
Aaron 2007	1 14	5 .	304	0.1%	2.25 [0.12, 43.76]	
Calverley 2007	217 309			15.5%	1.77 [1.43, 2.21]	-
Kardos 2007	23 50	7 7	487	1.4%	2.88 [1.39, 5.96]	
Calverley 2008	25 61	6 (	295	1.3%	1.85 [0.86, 3.98]	
Ferguson 2008	29 39			2.0%	1.93 [1.05, 3.54]	
Tashkin 2008	17 112			1.0%	1.45 [0.61, 3.44]	
Wedzicha 2008	50 65			3.4%	2.13 [1.33, 3.40]	
Anzueto 2009	26 39			1.7%	2.59 [1.33, 5.06]	
Rennard 2009	30 98			3.3%	0.73 [0.46, 1.18]	
Welte 2009	3 33			0.3%	0.99 [0.20, 4.95]	
Doherty 2012	16 71			1.0%	1.72 [0.73, 4.06]	<del></del>
Jung 2012	2 22			0.2%	1.04 [0.15, 7.44]	
Sharafkhaneh 2012	45 81			2.3%	1.89 [1.07, 3.34]	
Tashkin 2012 (1)	45 81			2.3%		<b></b>
					1.39 [0.65, 2.98]	<del></del>
Dransfield 2013	154 243 8 63			6.2%	1.78 [1.26, 2.51]	
Fukuchi 2013				0.7%	1.18 [0.43, 3.27]	
Kerwin 2013	12 61			0.9%	1.00 [0.41, 2.47]	
Martinez 2013	10 81			0.5%	2.13 [0.64, 7.12]	<b>—</b>
Magnussen 2014	72 124			6.4%	1.06 [0.75, 1.49]	
Ohar 2014	13 31			1.1%	1.36 [0.59, 3.12]	
Pepin 2014	3 12			0.1%	7.69 [0.79, 74.57]	
Wedzicha 2014	23 60			1.6%	2.05 [1.04, 4.05]	
Donohue 2015	8 70			0.5%	2.50 [0.76, 8.19]	
Zheng 2015	8 48			0.4%	0.65 [0.17, 2.40]	
Lee 2016	2 28			0.3%	0.51 [0.10, 2.55]	
Wedzicha 2016	80 168			6.2%	1.52 [1.08, 2.16]	
Ferguson 2017	3 60			0.4%	0.52 [0.14, 1.92]	
Papi 2017	40 117			2.1%	1.73 [0.96, 3.12]	
Vestbo 2017	40 161	4 19	1076	2.7%	1.39 [0.82, 2.36]	
Lipson 2018	609 828	5 97	2070	20.3%	1.52 [1.26, 1.84]	
Papi 2018	28 76	4 27	768	2.6%	1.04 [0.61, 1.79]	+
Rabe 2020	261 640			10.7%	1.68 [1.29, 2.19]	17
Subtotal (95% CI)	4086		24908		1.54 [1.42, 1.68]	♦
Total events	1896	68				
Heterogeneity: Chi <sup>2</sup> = 41.						
Test for overall effect: Z =						
. correr or brain on oot. 2 -		,				
Very severe COPD (GOI	D stage IV)					
	144 46	9 72	2 476	93.2%	2 42 [1 79 2 27]	
Calverley 2007 Wedzicha 2008					2.42 [1.78, 3.27]	<del>_</del>
	11 10			6.8%	4.50 [1.47, 13.80]	
Subtotal (95% CI)	56			100.0%	2.52 [1.88, 3.38]	•
Total events	155	74				
Heterogeneity: Chi <sup>2</sup> = 1.1			<b>b</b>			
Test for overall effect: Z =	6.19 (P < 0.000	01)				
						01 0.1 1 10 100
						Favours ICSs Favours Control
Test for subaroup differer	ces: Chi <sup>2</sup> = 20.1	l. df = 2 (l	<b>P</b> < 0.000	1). I <sup>2</sup> = 90	.1%	

	ICS	5	Cont	rol		Peto Odds Ratio	Peto Od	ds Ratio
Study or Subgroup					Weight	Peto, Fixed, 95% CI		ed, 95% Cl
< 65 years								
Vestbo 1999	16	145	24	145	2.8%	0.63 [0.32, 1.23]		-
Burge 2000	20	376	9	375	2.3%	2.19 [1.04, 4.61]		
Kardos 2007	23	507	7	487	2.4%	2.88 [1.39, 5.96]		
Tashkin 2008	17	1120	6	584	1.7%	1.45 [0.61, 3.44]	-	· · ·
Wedzicha 2008	22	311	8	315	2.3%	2.70 [1.30, 5.61]		
Rennard 2009	30	988	40	976	5.5%	0.73 [0.46, 1.18]	-	-
Welte 2009	3	331	3	329	0.5%	0.99 [0.20, 4.95]		
Calverley 2010	12	460	1	233	0.9%	3.26 [1.02, 10.41]		
Dransfield 2011	3	123	0	126	0.2%	7.70 [0.79, 74.69]	-	
Doherty 2012	16	717	6	479	1.7%	1.72 [0.73, 4.06]	-	<u> </u>
Hanania 2012	2	173	0	169	0.2%	7.26 [0.45, 116.60]		$\rightarrow$
Tashkin 2012 (1)	19	1351	9	900	2.2%	1.39 [0.65, 2.98]	-	
Tashkin 2012 (2)	7	634	3	421	0.8%	1.52 [0.43, 5.41]		
Dransfield 2013	154	2437	27	818	10.5%	1.78 [1.26, 2.51]		
Kerwin 2013	12	618	8	412	1.5%			
Martinez 2013			2	412		1.00 [0.41, 2.47]	_	
	10	816			0.9%	2.13 [0.64, 7.12]		
Vogelmeier 2013	4	264	0	258	0.3%	7.31 [1.02, 52.17]		-
Magnussen 2014	72	1243	68	1242	10.8%	1.06 [0.75, 1.49]		
Ohar 2014	13	314	10	325	1.8%	1.36 [0.59, 3.12]		
Wedzicha 2014	23	601	11	596	2.7%	2.05 [1.04, 4.05]		
Donohue 2015	8	701	3	702	0.9%	2.50 [0.76, 8.19]		
Singh 2015	0	358	1	358	0.1%	0.14 [0.00, 6.82]	· · · ·	
Zheng 2015	8	480	4	162	0.7%	0.65 [0.17, 2.40]		
Beeh 2016	2	431	3	436	0.4%	0.68 [0.12, 3.92]		
Covelli 2016	3	310	0	313	0.2%	7.51 [0.78, 72.46]	1	
Vogelmeier 2016	9	466	3	467	1.0%	2.76 [0.88, 8.61]	1	
Wedzicha 2016	80	1680	53	1678	10.4%	1.52 [1.08, 2.16]		
Ferguson 2017	3	605	6	613	0.7%	0.52 [0.14, 1.92]		
Papi 2017	40	1175	11	590	3.6%	1.73 [0.96, 3.12]	t	
Vestbo 2017	40	1614	19	1076	4.5%	1.39 [0.82, 2.36]	1	-
Ferguson 2018 (1)	16	1717	9	644	1.6%	0.64 [0.26, 1.55]		
Papi 2018	28	764	27	768	4.3%	1.04 [0.61, 1.79]	-	-
Huang 2019	1	293	0	289	0.1%	7.29 [0.14, 367.37]		· · · · ·
Kerwin 2019	6	282	8	174	1.0%	0.44 [0.15, 1.30]		-
Kerwin 2019			8 48	174 2125	1.0% 18.2%	0.44 [0.15, 1.30] 1.68 [1.29, 2.19]		- -
	6	282						•
Kerwin 2019 Rabe 2020	6	282 6404		2125	18.2%	1.68 [1.29, 2.19]		<b>.</b>
Kerwin 2019 Rabe 2020 Subtotal (95% CI)	6 261 983	282 6404 <b>30809</b>	48 437	2125 19993	18.2%	1.68 [1.29, 2.19]		•
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events	6 261 983 7.63, df = 3	282 6404 <b>30809</b> 4 (P = 0	48 437 .007); l² =	2125 19993	18.2%	1.68 [1.29, 2.19]		•
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 57	6 261 983 7.63, df = 3	282 6404 <b>30809</b> 4 (P = 0	48 437 .007); l² =	2125 19993	18.2%	1.68 [1.29, 2.19]		•
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 57	6 261 983 7.63, df = 3	282 6404 <b>30809</b> 4 (P = 0	48 437 .007); l² =	2125 19993	18.2%	1.68 [1.29, 2.19]		- ★
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 57 Test for overall effect: Z	6 261 983 7.63, df = 3	282 6404 <b>30809</b> 4 (P = 0	48 437 .007); l² =	2125 19993	18.2%	1.68 [1.29, 2.19]		•
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 57 Test for overall effect: Z ≥ 65 years	6 261 983 3.63, df = 3 = 6.28 (P •	282 6404 <b>30809</b> 4 (P = 0 < 0.0000	48 437 .007); I² = )1)	2125 <b>19993</b> = 41%	18.2% 100.0%	1.68 [1.29, 2.19] 1.43 [1.28, 1.60]		- •
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 57 Test for overall effect: Z ≥ 65 years Aaron 2007	6 261 983 3.63, df = 3 = 6.28 (P - 1	282 6404 <b>30809</b> 4 (P = 0 < 0.0000	48 437 .007); I <sup>2</sup> = 01) 1	2125 1 <b>9993</b> = 41% 304	18.2% 100.0% 0.1%	1.68 [1.29, 2.19] 1.43 [1.28, 1.60] 2.25 [0.12, 43.76]		- •
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 57 Test for overall effect: Z ≥ 65 years Aaron 2007 Calverley 2007	6 261 983 63, df = 3 = 6.28 (P - 1 217	282 6404 <b>30809</b> 4 (P = 0 < 0.0000 145 3098	48 437 .007); I <sup>2</sup> = 01) 1 124	2125 1 <b>9993</b> = 41% 304 3086	18.2% 100.0% 0.1% 16.8%	1.68 [1.29, 2.19] 1.43 [1.28, 1.60] 2.25 [0.12, 43.76] 1.77 [1.43, 2.21] 1.85 [0.86, 3.98]		- •
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 57 Test for overall effect: Z ≥ 65 years Aaron 2007 Calverley 2007 Calverley 2008	6 261 983 :.63, df = 3 = 6.28 (P - 1 217 25 28	282 6404 <b>30809</b> 4 (P = 0 < 0.0000 145 3098 616	48 437 .007); I <sup>2</sup> = 01) 1 124 6 16	2125 <b>19993</b> = 41% 304 3086 295 350	18.2% 100.0% 0.1% 16.8% 1.4% 2.1%	1.68 [1.29, 2.19] 1.43 [1.28, 1.60] 2.25 [0.12, 43.76] 1.77 [1.43, 2.21] 1.85 [0.86, 3.88] 1.80 [0.98, 3.32]		- •
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi² = 57 Test for overall effect: Z ≥ 65 years Aaron 2007 Calverley 2007 Calverley 2008 Wedzicha 2008 Anzueto 2009	6 261 983 (.63, df = 3 = 6.28 (P 1 217 25 28 28 26	282 6404 <b>30809</b> 4 (P = 0 < 0.0000 145 3098 616 347 394	48 437 .007); I <sup>2</sup> = 01) 1 124 6 16 10	2125 19993 = 41% 304 3086 295 350 403	18.2% 100.0% 0.1% 16.8% 1.4% 2.1% 1.8%	1.68 [1.29, 2.19] 1.43 [1.28, 1.60] 2.25 [0.12, 43.76] 1.77 [1.43, 2.21] 1.85 [0.86, 3.88] 1.80 [0.98, 3.32] 2.59 [1.33, 5.06]		- •
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi² = 57 Test for overall effect: Z ≥ 65 years Aaron 2007 Calverley 2007 Calverley 2007 Calverley 2008 Medzicha 2008 Anzueto 2009 Jung 2012	6 261 983 .63, df = 3 = 6.28 (P - 1 217 25 28 28 26 26 2	282 6404 <b>30809</b> 4 (P = 0 < 0.0000 145 3098 616 347 394 223	48 437 .007); I <sup>2</sup> = 01) 1 124 6 16 10 2	2125 19993 = 41% 304 3086 295 350 403 232	18.2% 100.0% 0.1% 16.8% 1.4% 2.1% 1.8% 0.2%	1.68 [1.29, 2.19] 1.43 [1.28, 1.60] 2.25 [0.12, 43.76] 1.77 [1.43, 2.21] 1.85 [0.86, 3.98] 1.80 [0.98, 3.32] 2.59 [1.33, 5.06] 1.04 [0.15, 7.44]		- - - 
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 57 Test for overall effect: Z ≥ 65 years Aaron 2007 Calverley 2007 Calverley 2007 Calverley 2008 Wedzicha 2008 Anzueto 2009 Jung 2012 Pepin 2014	6 261 983 63, df = 3 = 6.28 (P - 1 217 25 28 28 28 28 28 28 23	282 6404 <b>30809</b> 4 (P = 0 < 0.0000 145 3098 616 347 394 223 127	48 437 .007);  ² = )1) 124 6 16 16 10 2 0	2125 19993 41% 304 3086 295 350 403 232 130	18.2% 100.0% 0.1% 16.8% 1.4% 2.1% 1.8% 0.2% 0.2%	1.68 [1.29, 2.19] 1.43 [1.28, 1.60] 2.25 [0.12, 43.76] 1.77 [1.43, 2.21] 1.85 [0.86, 3.98] 1.80 [0.98, 3.32] 2.59 [1.33, 5.06] 1.04 [0.15, 7.44] 7.69 [0.79, 74.57]		- + - 
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 57 Test for overall effect: Z ≥ 65 years Aaron 2007 Calverley 2007 Calverley 2007 Calverley 2008 Wedzicha 2008 Anzueto 2009 Jung 2012 Pepin 2014 Rossi 2014	6 261 983 663, df = 3 = 6.28 (P - 1 217 25 28 26 26 2 3 2 3 2	282 6404 <b>30809</b> 4 (P = 0 < 0.0000 145 3098 616 347 394 223 127 288	48 437 .007);  ² = )1) 124 6 166 10 2 0 0	2125 19993 = 41% 304 3086 295 350 403 232 130 293	18.2% 100.0% 0.1% 16.8% 1.4% 2.1% 1.8% 0.2% 0.1%	1.68 [1.29, 2.19] 1.43 [1.28, 1.60] 2.25 [0.12, 43.76] 1.77 [1.43, 2.21] 1.85 [0.86, 3.98] 1.80 [0.98, 3.32] 2.59 [1.33, 5.06] 1.04 [0.15, 7.44] 7.69 [0.79, 74.57] 7.54 [0.47, 120.92]		- • • 
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi² = 57 Test for overall effect: Z ≥ 65 years Aaron 2007 Calverley 2007 Calverley 2008 Wedzicha 2008 Anzueto 2009 Jung 2012 Pepin 2014 Rossi 2014 Lee 2016	6 261 983 .63, df = 3 = 6.28 (P - 1 217 25 28 26 2 3 2 2 3 2 2 2 2	282 6404 <b>30809</b> 4 (P = 0 < 0.0000 145 3098 616 347 394 223 127 288 289	48 437 .007);  ² = 01) 124 6 16 10 2 0 0 4	2125 19993 41% 3086 295 350 403 232 130 293 289	18.2% 100.0% 0.1% 16.8% 1.4% 2.1% 1.8% 0.2% 0.1% 0.3%	1.68 [1.29, 2.19] 1.43 [1.28, 1.60] 2.25 [0.12, 43.76] 1.77 [1.43, 2.21] 1.85 [0.86, 3.88] 1.80 [0.98, 3.32] 2.59 [1.33, 5.06] 1.04 [0.15, 7.44] 7.69 [0.79, 74.57] 7.54 [0.47, 120.92] 0.51 [0.10, 2.55]		- - - - - - - - - - - - - -
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi² = 57 Test for overall effect: Z <b>≥ 65 years</b> Aaron 2007 Calverley 2007 Calverley 2008 Wedzicha 2008 Anzueto 2009 Jung 2012 Pepin 2014 Rossi 2014 Lee 2016 Vestbo 2016 (1)	6 261 983 .63, df = 3 = 6.28 (P - 1 217 25 28 26 26 2 3 2 2 3 2 2 465	282 6404 <b>30809</b> 4 (P = 0 < 0.0000 145 3098 616 347 394 223 127 288 289 8297	48 437 .007);  ² = )1) 1 124 6 16 10 2 0 0 0 4 377	2125 19993 41% 3086 295 350 403 232 130 293 289 8271	18.2% 100.0% 10.1% 16.8% 1.4% 2.1% 1.8% 0.2% 0.2% 0.2% 0.3% 41.6%	1.68 [1.29, 2.19] 1.43 [1.28, 1.60] 2.25 [0.12, 43.76] 1.77 [1.43, 2.21] 1.85 [0.86, 3.98] 1.80 [0.98, 3.32] 2.59 [1.33, 5.06] 1.04 [0.15, 7.44] 7.69 [0.79, 74.57] 7.54 [0.47, 120.92] 0.51 [0.10, 2.55] 1.24 [1.08, 1.43]		- - - - - - - - - - - - - -
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 57 Test for overall effect: Z ≥ 65 years Aaron 2007 Calverley 2007 Calverley 2007 Calverley 2008 Wedzicha 2008 Anzueto 2009 Jung 2012 Pepin 2014 Rossi 2014 Lee 2016 Vestbo 2016 (1) Vestbo 2016 (2)	6 261 983 .63, df = 3 = 6.28 (P - 1 217 25 28 26 2 3 2 2 3 2 2 465 94	282 6404 30809 4 (P = 0 < 0.0000 145 3098 616 347 394 223 127 288 8289 8297 1396	48 437 .007);  ² = 11) 124 6 16 16 10 2 0 0 4 377 83	2125 19993 441% 3086 295 350 403 232 130 293 289 8271 1403	18.2% 100.0% 10.1% 16.8% 1.4% 2.1% 1.8% 0.2% 0.2% 0.2% 0.1% 41.6% 8.6%	1.68 [1.29, 2.19] 1.43 [1.28, 1.60] 2.25 [0.12, 43.76] 1.77 [1.43, 2.21] 1.85 [0.86, 3.89] 1.80 [0.98, 3.32] 2.59 [1.33, 5.06] 1.04 [0.15, 7.44] 7.69 [0.79, 74.57] 7.54 [0.47, 120.92] 0.51 [0.10, 2.55] 1.24 [1.08, 1.43] 1.15 [0.85, 1.56]		- - - - - - - - - - - - - -
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Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 57 Test for overall effect: Z ≥ 65 years Aaron 2007 Calverley 2007 Calverley 2008 Wedzicha 2008 Anzueto 2009 Jung 2012 Pepin 2014 Rossi 2014 Lee 2016 Vestbo 2016 (1) Vestbo 2016 (2) Bhatt 2017 Siler 2017	6 261 983 3.63, df = 3 = 6.28 (P - 1 217 25 28 26 2 3 2 2 3 2 2 465 94 2 7	282 6404 30809 4 (P = 0 < 0.0000 145 3098 616 347 394 223 127 288 289 8297 1396 141 806	48 437 .007);  ² = 11) 1 124 6 16 16 10 2 0 0 4 377 83 3 7	2125 19993 41% 3086 295 350 403 232 130 293 289 8271 1403 303 814	18.2% 100.0% 0.1% 16.8% 1.4% 2.1% 1.8% 0.2% 0.1% 0.3% 41.6% 8.6% 0.2% 0.7%	1.68 [1.29, 2.19] 1.43 [1.28, 1.60] 2.25 [0.12, 43.76] 1.77 [1.43, 2.21] 1.85 [0.86, 3.98] 1.80 [0.98, 3.32] 2.59 [1.33, 5.06] 1.04 [0.15, 7.44] 7.69 [0.79, 74.57] 7.54 [0.47, 120.92] 0.51 [0.10, 2.55] 1.24 [1.08, 1.43] 1.15 [0.85, 1.56] 1.47 [0.22, 9.73] 1.01 [0.35, 2.89]		- - - - - - - - - - - - - -
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Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 57 Test for overall effect: Z $\geq$ 65 years Aaron 2007 Calverley 2007 Calverley 2008 Wedzicha 2008 Anzueto 2009 Jung 2012 Pepin 2014 Rossi 2014 Lee 2016 Vestbo 2016 (1) Vestbo 2016 (2) Bhatt 2017 Siler 2017 Betsuyaku 2018 Chapman 2018	6 261 983 .63, df = 3 = 6.28 (P - 1 217 25 28 26 26 2 3 2 2 2 465 94 2 7 6 9 9	282 6404 30809 4 (P = 0 < 0.0000 145 3098 616 347 394 223 127 288 8289 8297 1396 141 806 141 806 204 526	48 437 .007);  ² = 11) 124 6 6 16 10 2 0 0 0 4 377 83 3 7 6 6	2125 19993 41% 3086 295 350 403 232 130 293 289 8271 1403 303 814 201 527	18.2% 100.0% 10.1% 16.8% 1.4% 2.1% 1.8% 0.2% 0.2% 0.3% 41.6% 8.6% 0.2% 0.2% 0.6% 0.6% 0.8%	1.68 [1.29, 2.19] 1.43 [1.28, 1.60] 2.25 [0.12, 43.76] 1.77 [1.43, 2.21] 1.85 [0.86, 3.98] 1.80 [0.98, 3.32] 2.59 [1.33, 5.06] 1.04 [0.15, 7.44] 7.69 [0.79, 74.57] 7.54 [0.47, 120.92] 0.51 [0.10, 2.55] 1.24 [1.08, 1.43] 1.15 [0.85, 1.56] 1.47 [0.22, 9.73] 1.01 [0.35, 2.89] 0.98 [0.31, 3.10] 1.50 [0.54, 4.16]		- - - - - - - - - - - - - -
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 57 Test for overall effect: Z $\geq$ 65 years Aaron 2007 Calverley 2007 Calverley 2007 Calverley 2008 Wedzicha 2008 Medzicha 2008 Anzueto 2009 Jung 2012 Pepin 2014 Rossi 2014 Lee 2016 Vestbo 2016 (1) Vestbo 2016 (2) Bhatt 2017 Siler 2017 Siler 2017 Betsuyaku 2018 Chapman 2018 Ferguson 2018 (2)	6 261 983 3.63, df = 3 = 6.28 (P - 1 217 25 28 26 2 3 2 2 465 2 94 2 7 6 94 2 7 7 6 92	282 6404 30809 4 (P = 0 < 0.0000 145 3098 616 347 394 223 127 288 289 8297 1396 141 806 204 1271	48 437 .007);   <sup>2</sup> = 11) 124 6 166 16 10 2 0 0 4 377 83 3 7 6 6 6 10	2125 19993 41% 304 3086 295 350 403 232 130 293 8271 1403 303 814 201 527 625	18.2% 100.0% 10.1% 16.8% 2.1% 1.8% 0.2% 0.2% 0.3% 41.6% 8.6% 0.2% 0.7% 0.6% 0.8% 1.4%	$\begin{array}{c} 1.68 \left[ 1.29, 2.19 \right] \\ 1.43 \left[ 1.28, 1.60 \right] \\ \hline \\ 2.25 \left[ 0.12, 43.76 \right] \\ 1.77 \left[ 1.43, 2.21 \right] \\ 1.85 \left[ 0.86, 3.98 \right] \\ 1.80 \left[ 0.98, 3.32 \right] \\ 2.59 \left[ 1.33, 5.06 \right] \\ 1.04 \left[ 0.15, 7.44 \right] \\ 7.69 \left[ 0.79, 74.57 \right] \\ 7.54 \left[ 0.47, 120.92 \right] \\ 0.51 \left[ 0.10, 2.55 \right] \\ 1.24 \left[ 1.08, 1.43 \right] \\ 1.15 \left[ 0.85, 1.56 \right] \\ 1.47 \left[ 0.22, 9.73 \right] \\ 1.01 \left[ 0.35, 2.89 \right] \\ 0.98 \left[ 0.31, 3.10 \right] \\ 1.50 \left[ 0.54, 4.16 \right] \\ 1.08 \left[ 0.51, 2.28 \right] \end{array}$		
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 57 Test for overall effect: Z $\geq$ 65 years Aaron 2007 Calverley 2007 Calverley 2008 Wedzicha 2008 Anzueto 2009 Jung 2012 Pepin 2014 Rossi 2014 Lee 2016 Vestbo 2016 (1) Vestbo 2016 (2) Bhatt 2017 Siler 2017 Betsuyaku 2018 Chapman 2018	6 261 983 .63, df = 3 = 6.28 (P - 1 217 25 28 26 26 2 3 2 2 2 465 94 2 7 6 9 9	282 6404 30809 4 (P = 0 < 0.0000 145 3098 616 347 394 223 127 288 8289 8297 1396 141 806 141 806 204 526	48 437 .007);  ² = 11) 124 6 6 16 10 2 0 0 0 4 377 83 3 7 6 6	2125 19993 41% 3086 295 350 403 232 130 293 289 8271 1403 303 814 201 527	18.2% 100.0% 10.1% 16.8% 1.4% 2.1% 1.8% 0.2% 0.2% 0.3% 41.6% 8.6% 0.2% 0.2% 0.6% 0.6% 0.8%	1.68 [1.29, 2.19] 1.43 [1.28, 1.60] 2.25 [0.12, 43.76] 1.77 [1.43, 2.21] 1.85 [0.86, 3.98] 1.80 [0.98, 3.32] 2.59 [1.33, 5.06] 1.04 [0.15, 7.44] 7.69 [0.79, 74.57] 7.54 [0.47, 120.92] 0.51 [0.10, 2.55] 1.24 [1.08, 1.43] 1.15 [0.85, 1.56] 1.47 [0.22, 9.73] 1.01 [0.35, 2.89] 0.98 [0.31, 3.10] 1.50 [0.54, 4.16]		
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 57 Test for overall effect: Z $\geq$ 65 years Aaron 2007 Calverley 2007 Calverley 2007 Calverley 2008 Wedzicha 2008 Medzicha 2008 Anzueto 2009 Jung 2012 Pepin 2014 Rossi 2014 Lee 2016 Vestbo 2016 (1) Vestbo 2016 (2) Bhatt 2017 Siler 2017 Siler 2017 Betsuyaku 2018 Chapman 2018 Ferguson 2018 (2)	6 261 983 3.63, df = 3 = 6.28 (P - 1 217 25 28 26 2 3 2 2 465 2 94 2 7 6 94 2 7 7 6 92	282 6404 30809 4 (P = 0 < 0.0000 145 3098 616 347 394 223 127 288 289 8297 1396 141 806 204 1271	48 437 .007);   <sup>2</sup> = 11) 124 6 166 16 10 2 0 0 4 377 83 3 7 6 6 6 10	2125 19993 41% 304 3086 295 350 403 232 130 293 8271 1403 303 814 201 527 625	18.2% 100.0% 10.1% 16.8% 2.1% 1.8% 0.2% 0.2% 0.3% 41.6% 8.6% 0.2% 0.7% 0.6% 0.8% 1.4%	$\begin{array}{c} 1.68 \left[ 1.29, 2.19 \right] \\ 1.43 \left[ 1.28, 1.60 \right] \\ \hline \\ 2.25 \left[ 0.12, 43.76 \right] \\ 1.77 \left[ 1.43, 2.21 \right] \\ 1.85 \left[ 0.86, 3.98 \right] \\ 1.80 \left[ 0.98, 3.32 \right] \\ 2.59 \left[ 1.33, 5.06 \right] \\ 1.04 \left[ 0.15, 7.44 \right] \\ 7.69 \left[ 0.79, 74.57 \right] \\ 7.54 \left[ 0.47, 120.92 \right] \\ 0.51 \left[ 0.10, 2.55 \right] \\ 1.24 \left[ 1.08, 1.43 \right] \\ 1.15 \left[ 0.85, 1.56 \right] \\ 1.47 \left[ 0.22, 9.73 \right] \\ 1.01 \left[ 0.35, 2.89 \right] \\ 0.98 \left[ 0.31, 3.10 \right] \\ 1.50 \left[ 0.54, 4.16 \right] \\ 1.08 \left[ 0.51, 2.28 \right] \end{array}$		- + - - - - - - - - - - - - -
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 57 Test for overall effect: Z ≥ 65 years Aaron 2007 Calverley 2007 Calverley 2007 Calverley 2008 Wedzicha 2008 Anzueto 2009 Jung 2012 Pepin 2014 Rossi 2014 Lee 2016 Vestbo 2016 (1) Vestbo 2016 (2) Bhatt 2017 Siler 2017 Belsuyaku 2018 Chapman 2018 Ferguson 2018 (2) Frith 2018	6 261 983 3.63, df = 3 = 6.28 (P - 1 217 25 28 26 2 3 2 2 3 2 2 3 2 2 3 2 2 3 2 2 3 2 2 5 3 2 2 3 2 2 3 2 2 5 9 4 65 9 9 9 22 2 1	282 6404 30809 4 (P = 0 < 0.0000 145 3098 616 347 398 616 347 398 616 347 398 616 347 398 616 347 398 616 347 398 616 347 398 616 347 398 616 347 323 127 288 289 8297 1396 614 141 256	48 437 .007);  ² = 11) 1 124 6 16 16 10 2 0 0 4 377 8 3 3 7 6 6 6 0 10 1	2125 19993 41% 304 3086 295 350 403 232 130 293 289 8271 1403 303 814 201 527 625 248	18.2% 100.0% 100.0% 16.8% 1.4% 2.1% 1.8% 0.2% 0.1% 0.3% 41.6% 8.6% 0.2% 0.7% 0.6% 0.6% 0.8% 0.1%	$\begin{array}{c} 1.68 \left[ 1.29, 2.19 \right] \\ 1.43 \left[ 1.28, 1.60 \right] \\ \hline \\ 2.25 \left[ 0.12, 43.76 \right] \\ 1.77 \left[ 1.43, 2.21 \right] \\ 1.85 \left[ 0.86, 3.98 \right] \\ 1.80 \left[ 0.98, 3.32 \right] \\ 2.59 \left[ 1.33, 5.06 \right] \\ 1.04 \left[ 0.15, 7.44 \right] \\ 7.69 \left[ 0.79, 74.57 \right] \\ 7.54 \left[ 0.47, 120.92 \right] \\ 0.51 \left[ 0.10, 2.55 \right] \\ 1.24 \left[ 1.08, 1.43 \right] \\ 1.15 \left[ 0.85, 1.56 \right] \\ 1.47 \left[ 0.22, 9.73 \right] \\ 1.01 \left[ 0.35, 2.89 \right] \\ 0.98 \left[ 0.31, 3.10 \right] \\ 1.50 \left[ 0.54, 4.16 \right] \\ 1.08 \left[ 0.51, 2.28 \right] \\ 0.99 \left[ 0.06, 15.90 \right] \end{array}$		
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 57 Test for overall effect: Z $\geq$ 65 years Aaron 2007 Calverley 2007 Calverley 2007 Calverley 2008 Wedzicha 2008 Anzueto 2009 Jung 2012 Pepin 2014 Rossi 2014 Lee 2016 Vestbo 2016 (1) Vestbo 2016 (2) Bhatt 2017 Siler 2017 Betsuyaku 2018 Chapman 2018 Ferguson 2018 (2) Frith 2018 Lipson 2018	6 261 983 .63, df = 3 = 6.28 (P - 1 217 25 28 26 2 3 3 2 2 465 94 2 7 6 9 9 4 6 9 9 22 1 609 19	282 6404 30809 4 (P = 0 < 0.0000 145 3098 616 347 394 223 127 288 289 8297 1396 141 806 204 526 1271 250 8285	48 437 .007);  ² = 11) 124 6 6 16 10 2 0 0 0 4 377 83 3 7 6 6 6 6 10 1 97 5	2125 19993 41% 3086 295 350 403 232 130 293 289 8271 1403 303 814 201 527 625 248 2070 138	18.2% 100.0% 10.1% 16.8% 1.4% 2.1% 1.8% 0.2% 0.1% 0.3% 41.6% 8.6% 0.2% 0.6% 0.8% 1.4% 0.8% 1.4% 0.1% 21.9%	$\begin{array}{c} 1.68 \left[ 1.29, 2.19 \right] \\ 1.43 \left[ 1.28, 1.60 \right] \\ \hline \\ 2.25 \left[ 0.12, 43.76 \right] \\ 1.77 \left[ 1.43, 2.21 \right] \\ 1.85 \left[ 0.86, 3.98 \right] \\ 1.80 \left[ 0.98, 3.32 \right] \\ 2.59 \left[ 1.33, 5.06 \right] \\ 1.04 \left[ 0.15, 7.44 \right] \\ 7.69 \left[ 0.79, 74.57 \right] \\ 7.54 \left[ 0.47, 120.92 \right] \\ 0.51 \left[ 0.10, 2.55 \right] \\ 1.24 \left[ 1.08, 1.43 \right] \\ 1.15 \left[ 0.85, 1.56 \right] \\ 1.47 \left[ 0.22, 9.73 \right] \\ 1.01 \left[ 0.35, 2.89 \right] \\ 0.98 \left[ 0.31, 3.10 \right] \\ 1.50 \left[ 0.54, 4.16 \right] \\ 1.08 \left[ 0.51, 2.28 \right] \\ 0.99 \left[ 0.06, 15.90 \right] \\ 1.52 \left[ 1.26, 1.84 \right] \end{array}$		
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 57 Test for overall effect: Z $\geq$ 65 years Aaron 2007 Calverley 2007 Calverley 2008 Wedzicha 2008 Anzueto 2009 Jung 2012 Pepin 2014 Rossi 2014 Lee 2016 Vestbo 2016 (1) Vestbo 2016 (2) Bhatt 2017 Siler 2017 Betsuyaku 2018 Chapman 2018 Ferguson 2018 Chapman 2018 Lipson 2018 Ichinose 2019	6 261 983 .63, df = 3 = 6.28 (P - 1 217 25 28 26 2 3 3 2 2 465 94 2 7 6 9 9 4 6 9 9 22 1 609 19	282 6404 30809 4 (P = 0 < 0.0000 145 3098 616 347 394 223 127 288 289 8297 1396 141 806 204 526 1271 250 8285 278	48 437 .007);  ² = 11) 124 6 6 16 10 2 0 0 0 4 377 83 3 7 6 6 6 6 10 1 97 5	2125 19993 41% 3086 295 350 403 232 130 293 289 8271 1403 303 814 201 527 625 248 2070 138	18.2% 100.0% 10.1% 16.8% 1.4% 0.2% 0.2% 0.1% 0.1% 0.3% 41.6% 8.6% 0.2% 0.6% 0.8% 1.4% 0.1% 21.9% 21.9% 1.0%	$\begin{array}{c} 1.68 \left[ 1.29, 2.19 \right] \\ 1.43 \left[ 1.28, 1.60 \right] \\ \hline \\ 2.25 \left[ 0.12, 43.76 \right] \\ 1.77 \left[ 1.43, 2.21 \right] \\ 1.85 \left[ 0.86, 3.89 \right] \\ 1.80 \left[ 0.98, 3.32 \right] \\ 2.59 \left[ 1.33, 5.06 \right] \\ 1.04 \left[ 0.15, 7.44 \right] \\ 7.69 \left[ 0.79, 74.57 \right] \\ 7.54 \left[ 0.47, 120.92 \right] \\ 0.51 \left[ 0.10, 2.55 \right] \\ 1.24 \left[ 1.08, 1.43 \right] \\ 1.15 \left[ 0.85, 1.56 \right] \\ 1.47 \left[ 0.22, 9.73 \right] \\ 1.01 \left[ 0.35, 2.89 \right] \\ 0.98 \left[ 0.31, 3.10 \right] \\ 1.50 \left[ 0.54, 4.16 \right] \\ 1.08 \left[ 0.51, 2.28 \right] \\ 0.99 \left[ 0.06, 1.50 \right] \\ 1.52 \left[ 1.26, 1.84 \right] \\ 1.80 \left[ 0.75, 4.32 \right] \end{array}$		
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 57 Test for overall effect: Z ≥ 65 years Aaron 2007 Calverley 2007 Calverley 2007 Calverley 2008 Wedzicha 2008 Anzueto 2009 Jung 2012 Pepin 2014 Rossi 2014 Lee 2016 Vestbo 2016 (1) Vestbo 2016 (2) Bhatt 2017 Siler 2017 Betsuyaku 2018 Chapman 2018 Ferguson 2018 (2) Frith 2018 Lipson 2018 Ichinose 2019 Subtotal (95% CI) Total events	6 261 983 3.63, df = 3 = 6.28 (P - 1 217 25 28 26 26 2 2 3 2 2 465 94 2 7 6 9 9 4 2 7 7 6 9 9 4 2 1 609 19	282 6404 30809 4 (P = 0 < 0.0000 145 3098 616 347 398 616 347 223 127 288 289 8297 1396 141 806 204 1271 250 8285 278 26981	48 437 .007);   <sup>2</sup> = 11) 1 124 6 16 16 10 2 0 0 4 377 83 3 7 6 6 6 0 10 1 97 5 758	2125 19993 41% 3086 295 350 403 235 130 293 289 8271 1403 303 814 201 525 248 2070 138 19982	18.2% 100.0% 10.1% 16.8% 1.4% 0.2% 0.2% 0.1% 0.1% 0.3% 41.6% 8.6% 0.2% 0.6% 0.8% 1.4% 0.1% 21.9% 21.9% 1.0%	$\begin{array}{c} 1.68 \left[ 1.29, 2.19 \right] \\ 1.43 \left[ 1.28, 1.60 \right] \\ \hline \\ 2.25 \left[ 0.12, 43.76 \right] \\ 1.77 \left[ 1.43, 2.21 \right] \\ 1.85 \left[ 0.86, 3.89 \right] \\ 1.80 \left[ 0.98, 3.32 \right] \\ 2.59 \left[ 1.33, 5.06 \right] \\ 1.04 \left[ 0.15, 7.44 \right] \\ 7.69 \left[ 0.79, 74.57 \right] \\ 7.54 \left[ 0.47, 120.92 \right] \\ 0.51 \left[ 0.10, 2.55 \right] \\ 1.24 \left[ 1.08, 1.43 \right] \\ 1.15 \left[ 0.85, 1.56 \right] \\ 1.47 \left[ 0.22, 9.73 \right] \\ 1.01 \left[ 0.35, 2.89 \right] \\ 0.98 \left[ 0.31, 3.10 \right] \\ 1.50 \left[ 0.54, 4.16 \right] \\ 1.08 \left[ 0.51, 2.28 \right] \\ 0.99 \left[ 0.06, 1.50 \right] \\ 1.52 \left[ 1.26, 1.84 \right] \\ 1.80 \left[ 0.75, 4.32 \right] \end{array}$		
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 57 Test for overall effect: Z ≥ 65 years Aaron 2007 Calverley 2007 Calverley 2007 Calverley 2008 Wedzicha 2008 Anzueto 2009 Jung 2012 Pepin 2014 Rossi 2014 Lee 2016 Vestbo 2016 (1) Vestbo 2016 (2) Bhatt 2017 Siler 2017 Belsuyaku 2018 Chapman 2018 Ferguson 2018 (2) Frith 2018 Lipson 2018 Ichinose 2019 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 21	6 261 983 3.63, df = 3 = 6.28 (P - 1 217 25 28 26 2 3 2 2 465 94 2 7 6 9 22 1 609 19 1540 .02, df = 1	282 6404 30809 4 (P = 0 < 0.0000 145 3098 616 347 394 223 127 288 289 8297 1396 141 806 204 526 1271 250 8285 278 26981 8 (P = 0	48 437 .007);   <sup>2</sup> = 11) 1 1 124 6 16 10 2 0 0 4 377 83 3 7 6 6 10 0 1 97 5 758 .28);   <sup>2</sup> =	2125 19993 41% 3086 295 350 403 235 130 293 289 8271 1403 303 814 201 525 248 2070 138 19982	18.2% 100.0% 10.1% 16.8% 1.4% 0.2% 0.2% 0.1% 0.1% 0.3% 41.6% 8.6% 0.2% 0.6% 0.8% 1.4% 0.1% 21.9% 21.9% 1.0%	$\begin{array}{c} 1.68 \left[ 1.29, 2.19 \right] \\ 1.43 \left[ 1.28, 1.60 \right] \\ \hline \\ 2.25 \left[ 0.12, 43.76 \right] \\ 1.77 \left[ 1.43, 2.21 \right] \\ 1.85 \left[ 0.86, 3.89 \right] \\ 1.80 \left[ 0.98, 3.32 \right] \\ 2.59 \left[ 1.33, 5.06 \right] \\ 1.04 \left[ 0.15, 7.44 \right] \\ 7.69 \left[ 0.79, 74.57 \right] \\ 7.54 \left[ 0.47, 120.92 \right] \\ 0.51 \left[ 0.10, 2.55 \right] \\ 1.24 \left[ 1.08, 1.43 \right] \\ 1.15 \left[ 0.85, 1.56 \right] \\ 1.47 \left[ 0.22, 9.73 \right] \\ 1.01 \left[ 0.35, 2.89 \right] \\ 0.98 \left[ 0.31, 3.10 \right] \\ 1.50 \left[ 0.54, 4.16 \right] \\ 1.08 \left[ 0.51, 2.28 \right] \\ 0.99 \left[ 0.06, 1.50 \right] \\ 1.52 \left[ 1.26, 1.84 \right] \\ 1.80 \left[ 0.75, 4.32 \right] \end{array}$		
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 57 Test for overall effect: Z ≥ 65 years Aaron 2007 Calverley 2007 Calverley 2007 Calverley 2008 Wedzicha 2008 Anzueto 2009 Jung 2012 Pepin 2014 Rossi 2014 Lee 2016 Vestbo 2016 (1) Vestbo 2016 (2) Bhatt 2017 Siler 2017 Siler 2017 Siler 2017 Betsuyaku 2018 Chapman 2018 Ferguson 2018 (2) Frith 2018 Lipson 2018 Ichinose 2019 Subtotal (95% CI) Total events	6 261 983 3.63, df = 3 = 6.28 (P - 1 217 25 28 26 2 3 2 2 465 94 2 7 6 9 22 1 609 19 1540 .02, df = 1	282 6404 30809 4 (P = 0 < 0.0000 145 3098 616 347 394 223 127 288 289 8297 1396 141 806 204 526 1271 250 8285 278 26981 8 (P = 0	48 437 .007);   <sup>2</sup> = 11) 1 1 124 6 16 10 2 0 0 4 377 83 3 7 6 6 10 0 1 97 5 758 .28);   <sup>2</sup> =	2125 19993 41% 3086 295 350 403 235 130 293 289 8271 1403 303 814 201 525 248 2070 138 19982	18.2% 100.0% 10.1% 16.8% 1.4% 2.1% 1.8% 0.2% 0.1% 0.1% 0.3% 41.6% 8.6% 0.2% 0.6% 0.8% 1.4% 0.1% 21.9% 21.9%	$\begin{array}{c} 1.68 \left[ 1.29, 2.19 \right] \\ 1.43 \left[ 1.28, 1.60 \right] \\ \hline \\ 2.25 \left[ 0.12, 43.76 \right] \\ 1.77 \left[ 1.43, 2.21 \right] \\ 1.85 \left[ 0.86, 3.89 \right] \\ 1.80 \left[ 0.98, 3.32 \right] \\ 2.59 \left[ 1.33, 5.06 \right] \\ 1.04 \left[ 0.15, 7.44 \right] \\ 7.69 \left[ 0.79, 74.57 \right] \\ 7.54 \left[ 0.47, 120.92 \right] \\ 0.51 \left[ 0.10, 2.55 \right] \\ 1.24 \left[ 1.08, 1.43 \right] \\ 1.15 \left[ 0.85, 1.56 \right] \\ 1.47 \left[ 0.22, 9.73 \right] \\ 1.01 \left[ 0.35, 2.89 \right] \\ 0.98 \left[ 0.31, 3.10 \right] \\ 1.50 \left[ 0.54, 4.16 \right] \\ 1.08 \left[ 0.51, 2.28 \right] \\ 0.99 \left[ 0.06, 1.50 \right] \\ 1.52 \left[ 1.26, 1.84 \right] \\ 1.80 \left[ 0.75, 4.32 \right] \end{array}$		
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 57 Test for overall effect: Z ≥ 65 years Aaron 2007 Calverley 2007 Calverley 2007 Calverley 2008 Wedzicha 2008 Anzueto 2009 Jung 2012 Pepin 2014 Rossi 2014 Lee 2016 Vestbo 2016 (1) Vestbo 2016 (2) Bhatt 2017 Siler 2017 Belsuyaku 2018 Chapman 2018 Ferguson 2018 (2) Frith 2018 Lipson 2018 Ichinose 2019 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 21	6 261 983 3.63, df = 3 = 6.28 (P - 1 217 25 28 26 2 3 2 2 465 94 2 7 6 9 22 1 609 19 1540 .02, df = 1	282 6404 30809 4 (P = 0 < 0.0000 145 3098 616 347 394 223 127 288 289 8297 1396 141 806 204 526 1271 250 8285 278 26981 8 (P = 0	48 437 .007);   <sup>2</sup> = 11) 1 1 124 6 16 10 2 0 0 4 377 83 3 7 6 6 10 0 1 97 5 758 .28);   <sup>2</sup> =	2125 19993 41% 3086 295 350 403 235 130 293 289 8271 1403 303 814 201 525 248 2070 138 19982	18.2% 100.0% 10.1% 16.8% 1.4% 2.1% 1.8% 0.2% 0.1% 0.1% 0.3% 41.6% 8.6% 0.2% 0.6% 0.8% 1.4% 0.1% 21.9% 21.9%	$\begin{array}{c} 1.68 \left[ 1.29, 2.19 \right] \\ 1.43 \left[ 1.28, 1.60 \right] \\ \hline \\ 2.25 \left[ 0.12, 43.76 \right] \\ 1.77 \left[ 1.43, 2.21 \right] \\ 1.85 \left[ 0.86, 3.89 \right] \\ 1.80 \left[ 0.98, 3.32 \right] \\ 2.59 \left[ 1.33, 5.06 \right] \\ 1.04 \left[ 0.15, 7.44 \right] \\ 7.69 \left[ 0.79, 74.57 \right] \\ 7.54 \left[ 0.47, 120.92 \right] \\ 0.51 \left[ 0.10, 2.55 \right] \\ 1.24 \left[ 1.08, 1.43 \right] \\ 1.15 \left[ 0.85, 1.56 \right] \\ 1.47 \left[ 0.22, 9.73 \right] \\ 1.01 \left[ 0.35, 2.89 \right] \\ 0.98 \left[ 0.31, 3.10 \right] \\ 1.50 \left[ 0.54, 4.16 \right] \\ 1.08 \left[ 0.51, 2.28 \right] \\ 0.99 \left[ 0.06, 1.50 \right] \\ 1.52 \left[ 1.26, 1.84 \right] \\ 1.80 \left[ 0.75, 4.32 \right] \end{array}$		
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 57 Test for overall effect: Z ≥ 65 years Aaron 2007 Calverley 2007 Calverley 2007 Calverley 2008 Wedzicha 2008 Anzueto 2009 Jung 2012 Pepin 2014 Rossi 2014 Lee 2016 Vestbo 2016 (1) Vestbo 2016 (2) Bhatt 2017 Siler 2017 Belsuyaku 2018 Chapman 2018 Ferguson 2018 (2) Frith 2018 Lipson 2018 Lipson 2018 Ichinose 2019 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 21	6 261 983 3.63, df = 3 = 6.28 (P - 1 217 25 28 26 2 3 2 2 465 94 2 7 6 9 22 1 609 19 1540 .02, df = 1	282 6404 30809 4 (P = 0 < 0.0000 145 3098 616 347 394 223 127 288 289 8297 1396 141 806 204 526 1271 250 8285 278 26981 8 (P = 0	48 437 .007);   <sup>2</sup> = 11) 1 1 124 6 16 10 2 0 0 4 377 83 3 7 6 6 10 0 1 97 5 758 .28);   <sup>2</sup> =	2125 19993 41% 3086 295 350 403 235 130 293 289 8271 1403 303 814 201 525 248 2070 138 19982	18.2% 100.0% 10.1% 16.8% 1.4% 2.1% 1.8% 0.2% 0.1% 0.1% 0.3% 41.6% 8.6% 0.2% 0.6% 0.8% 1.4% 0.1% 21.9% 21.9%	$\begin{array}{c} 1.68 \left[ 1.29, 2.19 \right] \\ 1.43 \left[ 1.28, 1.60 \right] \\ \hline \\ 2.25 \left[ 0.12, 43.76 \right] \\ 1.77 \left[ 1.43, 2.21 \right] \\ 1.85 \left[ 0.86, 3.89 \right] \\ 1.80 \left[ 0.98, 3.32 \right] \\ 2.59 \left[ 1.33, 5.06 \right] \\ 1.04 \left[ 0.15, 7.44 \right] \\ 7.69 \left[ 0.79, 74.57 \right] \\ 7.54 \left[ 0.47, 120.92 \right] \\ 0.51 \left[ 0.10, 2.55 \right] \\ 1.24 \left[ 1.08, 1.43 \right] \\ 1.15 \left[ 0.85, 1.56 \right] \\ 1.47 \left[ 0.22, 9.73 \right] \\ 1.01 \left[ 0.35, 2.89 \right] \\ 0.98 \left[ 0.31, 3.10 \right] \\ 1.50 \left[ 0.54, 4.16 \right] \\ 1.08 \left[ 0.51, 2.28 \right] \\ 0.99 \left[ 0.06, 1.50 \right] \\ 1.52 \left[ 1.26, 1.84 \right] \\ 1.80 \left[ 0.75, 4.32 \right] \end{array}$		• • • • • • • • • • • • • • • • • • •
Kerwin 2019 Rabe 2020 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 57 Test for overall effect: Z ≥ 65 years Aaron 2007 Calverley 2007 Calverley 2007 Calverley 2008 Wedzicha 2008 Anzueto 2009 Jung 2012 Pepin 2014 Rossi 2014 Lee 2016 Vestbo 2016 (1) Vestbo 2016 (2) Bhatt 2017 Siler 2017 Belsuyaku 2018 Chapman 2018 Chapman 2018 Ferguson 2018 (2) Frith 2018 Lipson 2018 Lipson 2018 Ichinose 2019 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 21	6 261 983 3.63, df = 3 = 6.28 (P - 1 217 25 28 26 2 2 3 2 2 465 9 2 2 2 465 9 2 2 7 6 9 9 22 1 609 19 1540 .02, df = 1 = 7.53 (P -	282 6404 30809 4 (P = 0 < 0.0000 145 3098 616 347 398 616 347 223 127 288 289 8297 1396 141 806 204 526 1271 250 8285 278 26981 8 (P = 0 < 0.0000	48 437 .007);   <sup>2</sup> = 11) 1 124 6 16 10 2 0 0 4 377 83 3 7 6 6 10 1 97 5 758 .28);   <sup>2</sup> = 11)	2125 19993 41% 3086 295 350 403 232 130 293 289 8271 1403 814 201 527 625 248 2070 138 19982 14%	18.2% 100.0% 100.0% 16.8% 1.4% 2.1% 1.8% 0.2% 0.1% 0.3% 41.6% 8.6% 0.2% 0.7% 0.6% 0.6% 0.8% 0.1% 21.9% 1.0% 100.0%	$\begin{array}{c} 1.68 \left[ 1.29, 2.19 \right] \\ 1.43 \left[ 1.28, 1.60 \right] \\ \hline \\ 2.25 \left[ 0.12, 43.76 \right] \\ 1.77 \left[ 1.43, 2.21 \right] \\ 1.85 \left[ 0.86, 3.89 \right] \\ 1.80 \left[ 0.98, 3.32 \right] \\ 2.59 \left[ 1.33, 5.06 \right] \\ 1.04 \left[ 0.15, 7.44 \right] \\ 7.69 \left[ 0.79, 74.57 \right] \\ 7.54 \left[ 0.47, 120.92 \right] \\ 0.51 \left[ 0.10, 2.55 \right] \\ 1.24 \left[ 1.08, 1.43 \right] \\ 1.15 \left[ 0.85, 1.56 \right] \\ 1.47 \left[ 0.22, 9.73 \right] \\ 1.01 \left[ 0.35, 2.89 \right] \\ 0.98 \left[ 0.31, 3.10 \right] \\ 1.50 \left[ 0.54, 4.16 \right] \\ 1.08 \left[ 0.51, 2.28 \right] \\ 0.99 \left[ 0.06, 1.50 \right] \\ 1.52 \left[ 1.26, 1.84 \right] \\ 1.80 \left[ 0.75, 4.32 \right] \end{array}$		

	ICS	5	Conti	rol		Peto Odds Ratio		Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% C	l	Peto, Fixed, 95% Cl
: 25								
Burge 2000	20	376	9	375	24.3%	2.19 [1.04, 4.61]		
Vedzicha 2008	26	319	19	340	36.5%	1.49 [0.82, 2.74]		+=
lung 2012	2	223	2	232	3.5%	1.04 [0.15, 7.44]		
Zheng 2015	8	480	4	162	7.7%	0.65 [0.17, 2.40]		
.ee 2016	2	289	4	289	5.2%	0.51 [0.10, 2.55]		
Bhatt 2017	2	141	3	303	3.7%	1.47 [0.22, 9.73]		
rith 2018	1	250	1	248	1.7%	0.99 [0.06, 15.90]		
chinose 2019	19	278	5	138	17.5%	1.80 [0.75, 4.32]		
Subtotal (95% CI)		2356		2087	100.0%	1.47 [1.02, 2.12]		•
otal events	80		47					
leterogeneity: Chi <sup>2</sup> = 4			0); l² = 0%					
est for overall effect: Z	= 2.08 (P =	= 0.04)						
- OF								
≥ 25					_			
Aaron 2007	1	145	1	304	0.1%	2.25 [0.12, 43.76]		
Calverley 2007	217	3098	124	3086	15.3%	1.77 [1.43, 2.21]		
Calverley 2008	25	616	6	295	1.2%	1.85 [0.86, 3.98]		
erguson 2008	29	394	15	388	2.0%	1.93 [1.05, 3.54]		
Vedzicha 2008	24	339	4	325	1.3%	4.25 [1.99, 9.05]		
Anzueto 2009	26	394	10	403	1.6%	2.59 [1.33, 5.06]		
Velte 2009	3	331	3	329	0.3%	0.99 [0.20, 4.95]		
Dransfield 2011	3	123	0	126	0.1%	7.70 [0.79, 74.69]		
lanania 2012	2	173	0	169	0.1%	7.26 [0.45, 116.60]		
Dhar 2014	13	314	10	325	1.1%	1.36 [0.59, 3.12]		
Pepin 2014 Madaiaha 2014	3 23	127	0	130	0.1%	7.69 [0.79, 74.57]		
Vedzicha 2014 Donohue 2015		601 701	11 3	596	1.6%	2.05 [1.04, 4.05]		
Covelli 2016	8 3	310	0	702 313	0.5% 0.1%	2.50 [0.76, 8.19]		
/estbo 2016 (1)	3 465	8297	377	8271	38.0%	7.51 [0.78, 72.46]		
/estbo 2016 (2)	405 94	1396	83	1403	38.0% 7.9%	1.24 [1.08, 1.43] 1.15 [0.85, 1.56]		
/estbo 2017	94 40	1614	19	1403	2.6%	1.39 [0.82, 2.36]		<u> </u>
Chapman 2018	40 9	526	6	527	0.7%	1.50 [0.54, 4.16]		<b></b>
Ferguson 2018 (1)	16	1717	9	644	0.9%	0.64 [0.26, 1.55]		<del></del>
erguson 2018 (2)	22	1271	10	625	1.3%	1.08 [0.51, 2.28]		_ <b>_</b>
ipson 2018	609	8285	97	2070	20.0%	1.52 [1.26, 1.84]		+
Papi 2018	28	764	27	768	2.5%	1.04 [0.61, 1.79]		_ <b>_</b>
Cerwin 2019	6	282	8	174	0.6%	0.44 [0.15, 1.30]		— <del>—</del>
Subtotal (95% CI)	-	31818	-	23049	100.0%	1.43 [1.31, 1.55]		♦
Total events	1669		823					
leterogeneity: Chi <sup>2</sup> = 4		2 (P = 0		47%				
est for overall effect: Z				/0				
	0.10 (1	5.0000	,					
							<b>—</b>	
							0.01	0.1 1 10 10
Cost for subgroup differ	ences: Chi <sup>2</sup>	= 0.03	df = 1 (P)	= 0.86)	$l^2 = 0\%$			Favours ICSs Favours Control
est for subaroup differ								

body mass index) of patients would affect the incidence of pneumonia after ICSs treatment.

Our results first revealed that all types of ICSs significantly increased the pneumonia risk in COPD patients regardless of treatment duration. The dose-response relationship further confirmed the causality of ICSs treatment and increased pneumonia risk in COPD patients. Moreover, our results revealed that the pneumonia risk was related with COPD severity. However, age and BMI may not be the determinants of ICSs associated pneumonia. In addition, we found that COPD patients receiving different types of ICSs may have different risk of serious pneumonia. Only fluticasone increased the risk of serious pneumonia, while other types of ICSs did not. We speculated that this may be due to the different pharmacodynamics and pharmacokinetic characteristics of different types of ICSs. Previous studies reported that fluticasone could exhibit a longer retention in the airway mucosa and thus have a more prolonged suppression of local immunity of patients (Brattsand and Miller-Larsson, 2003; Dalby et al., 2009).

## **Compared With Other Studies**

Several previous meta-analyses (Sin et al., 2009; Singh et al., 2009; Kew and Seniukovich, 2014; Festic et al., 2016; Yang et al., 2019;

	ICSs		Contr			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl
Iuticasone							
Aaron 2007	1	145	1	304	0.3%	2.25 [0.12, 43.76]	
Ferguson 2008	19	394	10	388	5.1%	1.87 [0.89, 3.93]	
Nedzicha 2008	41	658	19	665	10.5%	2.18 [1.30, 3.66]	
Dransfield 2013	72	2437	8	818	10.8%	2.28 [1.37, 3.80]	
/ogelmeier 2013	2	264	0	258	0.4%	7.25 [0.45, 116.25]	
Betsuyaku 2018	4	204	0	201	0.7%	7.39 [1.03, 52.85]	
ipson 2018	336	8285	54	2070	44.0%	1.49 [1.16, 1.92]	
Subtotal (95% CI)		12387		4704	71.8%	1.75 [1.44, 2.14]	•
Total events	475		92				
Heterogeneity: Chi <sup>2</sup> = 6.39	9, df = 6 (P	= 0.38)	l² = 6%				
Test for overall effect: Z =	5.55 (P < 0	0.00001	)				
Budesonide							
Burge 2000	16	370	8	368	4.3%	1.98 [0.88, 4.46]	<u>⊢</u>
Fashkin 2008	8	1120	2	584	1.6%	1.89 [0.51, 7.00]	
Sharafkhaneh 2012	17	815	7	403	3.8%	1.20 [0.51, 2.83]	
Ferguson 2017	0	605	5	613	0.9%	0.14 [0.02, 0.79]	· · · · · · · · · · · · · · · · · · ·
Ferguson 2018 (1)	12	1717	6	644	2.6%	0.74 [0.26, 2.08]	
Kerwin 2019	2	282	4	174	1.0%	0.29 [0.06, 1.54]	
Subtotal (95% CI)		4909		2786	14.3%	1.06 [0.68, 1.65]	<b>•</b>
Total events	55		32				
Heterogeneity: Chi <sup>2</sup> = 11.	11, df = 5 (F	P = 0.05	);   <sup>2</sup> = 55 <sup>6</sup>	%			
Test for overall effect: Z =	0.24 (P = 0	0.81)	<ul> <li>Totol</li> </ul>				
Beclomethasone diprop	ionate						
/estbo 2017	30	1614	14	1076	7.6%	1.41 [0.77, 2.60]	+
Papi 2018	18	764	17	768	6.3%	1.07 [0.55, 2.08]	
Subtotal (95% CI)		2378		1844	13.9%	1.24 [0.79, 1.95]	◆
Total events	48		31				
Heterogeneity: Chi <sup>2</sup> = 0.3	7. df = 1 (P	= 0.54)	$ ^2 = 0\%$				
Test for overall effect: Z =		/					
Fotal (95% CI)		19674		9334	100.0%	1.55 [1.31, 1.84]	•
Fotal events	578		155				
Heterogeneity: Chi <sup>2</sup> = 23. <sup>-</sup>		(P = 0.0)		9%			
Fest for overall effect: Z =		•					0.01 0.1 1 10 10
			/				Favours ICSs Favours Control

Zhang et al., 2020) also assessed the pneumonia risk associated with ICSs treatment. However, there were major differences between our meta-analysis and the previous ones in terms of selected studies, statistical analyses, and outcomes. First, we included data of some recent large-scale RCTs (Bhatt et al., 2017; Papi et al., 2017; Siler et al., 2017; Vestbo et al., 2017; Betsuyaku et al., 2018; Chapman et al., 2018; Ferguson et al., 2018a; Ferguson et al., 2018b; Frith et al., 2018; Lipson et al., 2018; Papi et al., 2018; Ichinose et al., 2019; Kerwin et al., 2019; Rabe et al., 2020) which were published after some of the previous meta-analyses. In addition, varied search strategy may be an important reason for the difference in the number of RCTs included in different meta-analyses. We systematically searched four large databases for relevant RCTs, including PubMed, Embase, Cochrane Library, and Clinical Trials.gov. In particular, we systematically searched the online supplementary documents of relevant RCTs. Indeed, pneumonia risk was not the primary outcome in most RCTs,

some researchers provided data on pneumonia risk in the online supplementary documents rather than in the text. Second, compared with the previous meta-analyses, we conducted more subgroup analyses based on the baseline demographic characteristics of the patients (severity, age and BMI) to clarify possible varied pneumonia risk in different patients receiving ICSs treatment. Third, our results indicated that all types of ICSs, not only fluticasone, increase the pneumonia risk in COPD patients in a dose-dependent manner, and the risk is particularly evident in more severe patients.

In 2009, Singh et al. (Singh et al., 2009) performed a metaanalysis (18 RCTs, 16,996 patients) and concluded that ICSs (fluticasone and budesonide) treatment significantly increased the pneumonia risk in COPD patients. However, their study failed to provide some important information on ICSs associated pneumonia due to a lack of subgroup analyses based on medication details of ICSs (including dose, type and treatment duration), and subgroup analyses based on the baseline

Inhaled Corticosteroids and Pneumonia Risk

demographic characteristics of patients. In 2009, Sin et al. conducted a meta-analysis of budesonide and pneumonia risk (seven RCTs, 7,042 patients) and found that budesonide treatment for 12 mo did not increase the pneumonia risk in COPD patients. In 2014, a meta-analysis performed by Kew et al. (Kew and Seniukovich, 2014) (43 RCTs, 31,397 patients) suggested that both fluticasone and budesonide increased the serious pneumonia risk in COPD patients. However, that study did not further examine the association between other types of ICSs (momethasone and beclomethasone) and the pneumonia risk, nor conduct subgroup analyses based on the baseline demographic characteristics of patients. In 2016, another meta-analysis (29 RCTs, 33,472 patients) performed by Festic et al. (Festic et al., 2016) also revealed that ICSs increased the pneumonia risk in COPD patients. However, that study also limited by a smaller sample size and absent subgroup analyses. In addition, Yang et al. (Yang et al., 2019) conducted a metaanalysis (25 RCTs, 49,982 patients) and found ICSs significantly increased the pneumonia risk and serious pneumonia risk in COPD patients. However, their study also did not analyse the impact of baseline demographic characteristics of patients on the pneumonia risk. Moreover, in 2020, a meta-analysis (18 RCTs, 49,828 patients) performed by Zhang et al. (Zhang et al., 2020) also investigated the association between different types of ICSs and the pneumonia risk, and suggested that fluticasone increased the pneumonia risk while budesonide or beclomethasone did not. However, their results might be limited by the smaller sample size, since much fewer RCTs (especially RCTs on budesonide and beclomethasone) were included in their meta-analysis. In contrast, we searched more databases, used more search terms, and put less restrictions on literature search, which made more relevant RCTs were identified.

### **Limitations and Strengths**

The major strength of our study was that we conducted a comprehensive literature search including all currently available RCTs, thus ensured the generalizability of the conclusions. Moreover, the multiple subgroup analyses based on the medication details (dose and treatment duration) and baseline of patients (severity, age and BMI of patients) enhanced the reliability of the conclusions, and also provided implications for the clinical practice. As far as we know, our study is the first meta-analysis which systematically assesses the association between various types of ICSs and the pneumonia risk based on baseline characteristics of patients.

This meta-analysis had several limitations. First, none of the included RCTs were specifically designed to monitor pneumonia event, therefore, there may be underreporting of pneumonia incidence. However, the underestimate of the pneumonia risk could not substantially impact the pooled results of this metaanalysis, since underreporting of pneumonia incidence might occur equally in ICSs treatment groups and non-ICSs treatment groups. Moreover, in the sensitivity analysis, after removing four non double-blind RCTs, the results were consistent with the previous pooled results. Second, the pooled results of momethasone (four RCTs, 5,413 patients) and beclomethasone (four RCTs, 5,884 patients) may weakened by the relatively small sample size. Third, some studies were excluded because of incomplete data or non-English literature, which may lead to inevitable selection bias.

# CONCLUSIONS

ICSs treatment significantly increased the risk of pneumonia in COPD patients. There was a dose-response relationship between ICSs treatment and pneumonia risk. The pneumonia risk was related with COPD severity.

## DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/ Supplementary Material.

# **AUTHOR CONTRIBUTIONS**

HC and HY conceived and designed this study. HC and JS searched and selected studies. QH and YL extracted essential information. HC and MY assessed the risk of bias. HC and CM conducted the statistical analysis. HC wrote the original draft. All authors approved the final version to be published.

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# SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.691621/full#supplementary-material

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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