SUPPLEMENTARY MATERIAL

Systematic review on long-term adverse effects of inhaled corticosteroids in the treatment of chronic obstructive pulmonary disease

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Table S2: Characteristics of included studies

<u>**Randomized clinical trials**</u>

Study ID	Aaron 2007
Study acronym	OPTIMAL
Reference	Aaron, S. D., Vandemheen, K. L., Fergusson, D., Maltais, F., Bourbeau, J., Goldstein, R., ... & Bishop, G. (2007). Tiotropium in combination with placebo, salmeterol, or fluticasone–salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. Annals of internal medicine, 146(8), 545-555.
Sponsor	Canadian Institutes of Health Research Ontario Thoracic Society
Country	Canada
Objective	To determine whether combining tiotropium with salmeterol or fluticasone–salmeterol improves clinical outcomes in adults with moderate to severe COPD compared with tiotropium alone.
Setting	27 academic and community medical centres in Canada (20 were academic hospital– based pulmonary clinics, 5 were community-based pulmonary clinics, and 2 were community-based primary care clinics)
Design	**Clinical Trial -** Randomized, double-blind, placebo-controlled trial
Study period	October 2003 to January 2006.

Follow-up duration	1 year
Data source	NA
POPULATION (eligibility)	Patients with diagnosed moderate or severe COPD. Eligible patients had to have had at least 1 exacerbation of COPD that required treatment with systemic steroids or antibiotics within the 12 months before randomization. Additional inclusion criteria were age older than 35 years; a history of 10 pack-years or more of cigarette smoking; and documented chronic airflow obstruction, with an FEV1–FVC ratio less than 0.70 and a postbronchodilator FEV1 less than 65% of the predicted value. We excluded patients with a history of physician-diagnosed asthma before 40 years of age; those with a history of physician-diagnosed chronic congestive heart failure with known persistent severe left ventricular dysfunction; those receiving oral prednisone; those with a known hypersensitivity or intolerance to tiotropium, salmeterol, or fluticasone–salmeterol; those with a history of severe glaucoma or severe urinary tract obstruction, previous lung transplantation or lung volume reduction surgery, or diffuse bilateral bronchiectasis; and those who were pregnant or were breastfeeding. Persons with a recent COPD exacerbation requiring oral or intravenous antibiotics or steroids were required to wait until treatment with these agents had been discontinued for 28 days before entering the study.
POPULATION (baseline participant characteristics)	N=449 **Time since diagnosis:** Duration of reported dyspnea, y (SD) 10.78 (8.54) **Severity of condition:** % predicted FEV1 38.70 (12.65) **BMI:** 27.53 (6.00) **Current smoker %:** 27.82 **Sex (% women):** 43.70% **Age:** 67.74 (8.68) **Socioeconomic characteristics:** (white %) 98.21 **Previous medication (ICS) use (%):** Combination ICS/LABA: 47.26, ICS: 29.05
Evaluated ICS	Fluticasone
Number of cohorts	n=3 (Tiotropium + placebo (N=156), Tiotropium + Salmeterol (N=148) and **Tiotropium + Fluticasone–Salmeterol** (N=145))

Intervention (ICS)	Tiotropium, 18 ug once daily, plus fluticasone–salmeterol, 250/25 ug/puff, 2 puffs twice daily.
Intervention (Control)	Tiotropium, 18 ug once daily Tiotropium, 18 ug once daily, plus salmeterol 25 ug/puff, 2 puffs twice daily
Adjustment method	NA
Included Outcome/s	Pneumonia*, Oral Candidiasis and Dysphonia ***Pneumonia leading to mechanical ventilation or death**

Study ID	**Anzueto 2009**
Study acronym	**SCO100250**
Reference	Anzueto, A., Ferguson, G. T., Feldman, G., Chinsky, K., Seibert, A., Emmett, A., ... & Crater, G. (2009). Effect of fluticasone propionate/salmeterol (250/50) on COPD exacerbations and impact on patient outcomes. COPD: Journal of Chronic Obstructive Pulmonary Disease, 6(5), 320-329.
Sponsor	GlaxoSmithKline
Country	USA and Canada
Objective	To evaluate the effect of fluticasone propionate/salmeterol 250/50 on moderate/severe COPD exacerbations in subjects with a history of exacerbation(s) and its impact on patient related outcomes
Setting	98 research sites in the United States and Canada
Design	**Clinical Trial -** Randomized, double-blind, parallel-group study
Study period	NR
Follow-up duration	52 weeks
Data source	NA
POPULATION (eligibility)	Subjects were ≥ 40 years of age with a diagnosis of COPD (chronic bronchitis and/or emphysema), a cigarette smoking history ≥ 10 pack-years, a pre-albuterol FEV1/FVC ≤ 0.70, a FEV1 ≤ 50% of predicted normal and a documented history of at least 1 COPD exacerbation the year prior to the study that required treatment with antibiotics, oral corticosteroids, and/or hospitalization. Subjects were excluded if they had a current diagnosis of asthma, a respiratory disorder other than COPD, historical or current evidence of a clinically significant uncontrolled disease or had a COPD exacerbation that was not resolved at screening.

POPULATION (baseline participant characteristics)	N=797
	Time since diagnosis: NR
	Severity of condition: Post-bronchodilator FEV1, % predicted: 40.59 ± 13.5 40.0 ± 12.6
	Presence of other condition:
	BMI: 27.45 (6.41)
	Current smoker %: 42.5
	Smoking history, pack-years: 57.14 (30.32)
	Sex (% male): 54.03
	Age: 65.35 (8.95)
	Socioeconomic characteristics: (% white) 97.5
Evaluated ICS	Fluticasona
Number of cohorts	N=2 (Fluticasone propionate (FP) + Salmeterol (S) (N = 394) and Salmeterol (S) (N = 403))
Intervention (ICS)	FP: 500 mcg + S: 50 mcg, twice-daily via DISKUS for 52 weeks
Intervention (Control)	S: 50 mcg, twice-daily via DISKUS for 52 weeks
Adjustment method	NA
Included Outcome/s	Pneumonia, Oral Candidiasis, URTI, Dysphonia, Eye disorders, BMD

Study ID	**Bakerly 2019**
Study acronym	**SLS COPD (The Salford Lung Study)**
Reference	Bakerly, N.D., Woodcock, A., New, J.P. et al. The Salford Lung Study protocol: a pragmatic, randomised phase III real-world effectiveness trial in chronic obstructive pulmonary disease. Respir Res 16, 101 (2015). https://doi.org/10.1186/s12931-015-0267-6 J. Vestbo, D. Leather, N. Diar Bakerly, J. New, J.M. Gibson, S. McCorkindale, S. Collier, J. Crawford, L. Frith, C. Harvey, H. Svedsater, A. Woodcock, Salford Lung Study investigators, Effectiveness of fluticasone furoate-vilanterol for COPD in clinical practice, N. Engl. J. Med. 375 (2016) 1253–1260. Bakerly, N. D., Woodcock, A., Collier, S., Leather, D. A., New, J. P., Crawford, J., ... & Boucot, I. (2019). Benefit and safety of fluticasone furoate/vilanterol in the Salford Lung Study in chronic obstructive pulmonary disease (SLS COPD) according to baseline patient characteristics and treatment subgroups. Respiratory medicine, 147, 58-65.
Sponsor	GlaxoSmithKline

Country	United Kingdom
Objective	To evaluate the comparative effectiveness and safety of initiating fluticasone furoate/vilanterol (FF/VI) versus continuing UC in different predefined subgroups of patients with COPD
Setting	All patients with COPD at 75 primary care sites in and around Salford and South Manchester are identified by their general practitioner (GP) from practice databases and invited to participate in the study.
Design	**Clinical Trial -** Open-label, phase III pRCT
Study period	March 13, 2012 to October 23, 2014
Follow-up duration	12 months
Data source	NA
POPULATION (eligibility)	Patients aged ≥ 40 years, with a documented general practitioner's diagnosis of COPD, who had experienced ≥ 1 exacerbation of COPD within the previous 3 years, and taking regular maintenance inhaler therapy Minimal exclusion criteria: an exacerbation within the previous 2 weeks, chronic oral corticosteroid use.
POPULATION (baseline participant characteristics)	N= 2799 **Time since diagnosis:** more than 5 years (53%) **Severity of condition:** No. of exacerbations during the 12 mon before randomization 2.01 (1.99), GOLD grade 3 or 4 n: 547 **Presence of other condition:** **BMI:** 28 (6.00) **Current smoker n (%):** 1289 (46) **Any coexisting condition n (%):** 2145 (77) **Vascular condition n(%):** 1363 (49) **Diabetes n(%):** 438 (16) **Sex:** Female n (%): 1369 (49) **Age:** 67 (10) **Socioeconomic characteristics:** NR **Other:** A total of 762 patients (34%) were receiving inhaled glucocorticoids, a combination of inhaled glucocorticoids and a LABA, or a combination of inhaled glucocorticoids and a LAMA; 119 of these patients were using inhaled glucocorticoids as monotherapy. A total of 1231 patients (54%) were receiving

	combination triple therapy with inhaled glucocorticoids, a LABA, and a LAMA.
Evaluated ICS	Fluticasona
Number of cohorts	N=2 (Fluticasone furoate–vilanterol (N = 1396) and Usual-care group (N = 1403))
Intervention (ICS)	Combination therapy with 100 μg of fluticasone furoate and 25 μg of vilanterol (Relvar [in Europe] or Breo [in the United States], GlaxoSmithKline), administered once daily as a dry powder through an inhaler (Ellipta, GlaxoSmithKline) (the fluticasone furoate–vilanterol group)
Intervention (Control)	Continuation of usual care as determined by the general practitioner (the usual-care group)
Adjustment method	Patients were stratified according to maintenance therapy at baseline Stratum 1: LABA, LAMA or LABA + LAMA (n = 276, 12%) Stratum 2: ICS, ICS + LABA or ICS + LAMA (n = 762, 34%) Stratum 3: ICS + LABA + LAMA (n = 1231, 54%)
Included Outcome/s	Pneumonia, LRTI, HTA, BMD, Eye disorder, Diabetes

Study ID	**Brook 2017 (Vestbo 2016a)**
Study acronym	**SUMMIT** **"Study to Understand Mortality and Morbidity in COPD"**
Reference	Vestbo J, Anderson J, Brook RD, et al. The study to understand mortality and morbidity in COPD (SUMMIT) study protocol. Eur Respir J 2013;41:1017–22. Vestbo J, Anderson J, Brook RD, et al; SUMMIT Investigators. Fluticasone furoate and vilanterol in patients with chronic obstructive pulmonary disease at heightened cardiovascular risk. Lancet 2016;387:1817–26. Crim, C., Calverley, P. M., Anderson, J. A., Holmes, A. P., Kilbride, S., Martinez, F. J., ... & Vestbo, J. (2017). Pneumonia risk with inhaled fluticasone furoate and vilanterol in COPD patients with moderate airflow limitation: The SUMMIT trial. Respiratory medicine, 131, 27-34. Brook, R. D., Anderson, J. A., Calverley, P. M., Celli, B. R., Crim, C., Denvir, M. A., ... & Yates, J. (2017). Cardiovascular outcomes with an inhaled beta2-agonist/corticosteroid in patients with COPD at high cardiovascular risk. Heart, 103(19), 1536-1542.
Sponsor	GlaxoSmithKline
Country	Multinational (43 countries)

Objective	to assess whether inhaled treatment with a combined treatment of the corticosteroid, fluticasone furoate, and the long-acting β agonist, vilanterol could improve survival compared with placebo in patients with moderate COPD and heightened cardiovascular risk.
Setting	Patients treated on an outpatient basis and clinic visits.
Design	**Clinical Trial** Prospective double-blind parallel group placebo-controlled event-driven randomised trial conducted at 1368 centres in 43 countries. (NCT01313676)
Study period	Between Jan 24, 2011, and March 12, 2014
Follow-up duration	Mean exposure to study medication was 1.7 years. This was an event-driven study in which follow-up continued until at least 1000 deaths had occurred… The common end date was set at Jan 25, 2015.
Data source	NA
POPULATION (eligibility)	Patients who were current or former smokers with at least a 10-pack-year history. Eligible patients were aged 40–80 years and had a post-bronchodilator forced expiratory volume in 1 s (FEV1) between 50% and 70% (inclusive) of the predicted value, a ratio of post-bronchodilator FEV1 to forced vital capacity (FVC) of 0·70 or less, and a score of 2 or greater on the modified Medical Research Council dyspnoea scale. Patients had to have a history, or be at increased risk, of cardiovascular disease. Exclusion criteria included respiratory disorders other than COPD, lung reduction surgery, receiving long-term oxygen, or oral corticosteroid therapy, severe heart failure (New York Heart Association Class IV or ejection fraction <30%), life expectancy less than 3 years, and end-stage chronic renal disease.
POPULATION (baseline participant characteristics)	N= 16485 included in intention-to-treat efficacy (ITT) population **Time since diagnosis:** NR **Severity of condition:** % predicted FEV1 60 (±6) Presence of other condition: Three-quarters of patients had established cardiovascular disease or diabetes mellitus with end-organ disease (n=11 662 [71%]), whereas a quarter (n=4641 [28%]) had an increased risk of cardiovascular disease only. **BMI:** 28 (±6) Current smokers 47% (pack-year 41 (±25)) **Sex:** (female) n=4196 (25%) **Age:** 65 (8)

	Socioeconomic characteristics: Race White 13 357 (81%) Asian 2724 (17%) Other 404 (2%) **Other:** Pre-study COPD therapy Inhaled corticosteroid 1349 (33%) 1369 (33%) 1374 (33%) 1394 (34%)
Evaluated ICS	Fluticasona
Number of cohorts	N=4 (placebo group (N = 4111), **fluticasone furoate group** (N = 4135), vilanterol group (N = 4118) and **combination group** (N = 4121))
Intervention (ICS)	Fluticasone furoate [100 µg; GlaxoSmithKline], or the combination of fluticasone furoate and vilanterol [100/25 µg; Relvar/Breo,GlaxoSmithKline]
Intervention (Control)	placebo or vilanterol [25 µg; GlaxoSmithKline] given once daily as a dry powder with the use of an inhaler [Ellipta, GlaxoSmithKline]).
Adjustment method	The time to first pneumonia was compared between treatment groups using Kaplan Meier estimates and the Cox Proportional Hazards model (PH) including covariates of age and gender; for the analysis of the composite endpoint a covariate of previous exacerbations (exacerbations in the year prior to the study as 0, 1, >2) was also included.
Included Outcome/s	Pneumonia, LRTI, HTA, Fracture, BMD, Eye disorder, Diabetes, Adrenal supp. [Outcomes from Vestbo 2016a and Crim 2017]

Study ID	**Burge 2000**
Study acronym	**ISOLDE**
Reference	Burge, P. S., Calverley, P. M. A., Jones, P. W., Spencer, S., Anderson, J. A., & Maslen, T. K. (2000). Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. Bmj, 320(7245), 1297-1303.
Sponsor	GlaxoWellcome Research and Development.
Country	United Kingdom
Objective	To determine the effect of long-term inhaled corticosteroids on lung function, exacerbations, and health status in patients with moderate to severe chronic obstructive pulmonary disease
Setting	18 UK hospitals
Design	**Clinical Trial -** Double blind, placebo-controlled study.
Study period	October 1992 to 31 March 1995
Follow-up duration	3 years
Data source	NA

POPULATION (eligibility)	Patients were current or former smokers aged 40--75 years with non--asthmatic chronic obstructive pulmonary disease. Baseline FEV1 after bronchodilator was at least 0.8 litres but less than 85% of predicted normal, and the ratio of FEV1 to forced vital capacity was less than 70%. Previous use of inhaled and oral corticosteroids was permitted.
	Patients were excluded if their FEV1 response to 400 ìg salbutamol exceeded 10% of predicted normal, they had a life expectancy of less than five years from concurrent diseases, or they used â blockers. Nasal and ophthalmic corticosteroids, theophyllines, and all other bronchodilators were allowed -during the study.
POPULATION (baseline participant characteristics)	N=751
	Time since diagnosis: NR
	Severity of condition: FEV1 after bronchodilator (salbutamol 400 ìg and ipratropium bromide 80 ìg) 1.41 (0.48)
	BMI: 24.70 (4.75)
	Evidence of atopy: n=194
	Smoked throughout trial: n=284
	Sex (women): n=191
	Age: 63.75 (7.1)
	Socioeconomic characteristics: NR
	Other: Previous use of regular inhaled corticosteroids: n=406
Evaluated ICS	Fluticasona
Number of cohorts	N=2 (Fluticasone propionate (N = 376) and Placebo (N = 375))
Intervention (ICS)	Fluticasone propionate (FP): 500 µg twice daily administered from a metered dose inhaler and with a spacer device by using 10 tidal breaths after each of two actuations
Intervention (Control)	Placebo
Adjustment method	NA
Included Outcome/s	Oral Candidiasis, Fracture, Eye disorders and Dysphonia

Study ID	**Calverley 2003a**
Study acronym	**NA**
Reference	Calverley, P. M., Boonsawat, W., Cseke, Z., Zhong, N., Peterson, S., & Olsson, H. (2003). Maintenance therapy with budesonide and formoterol in chronicobstructive pulmonary disease. European Respiratory Journal, 22(6), 912-919.

Sponsor	AstraZeneca
Country	Multinational (15 countries)
Objective	To test a clinically relevant situation, namely whether the short-term improvement that follows a period of treatment optimisation can be maintained over a longer time by inhaled therapy, and to investigate which drugs change what aspect of patient well-being.
Setting	Outpatients from 109 centres in 15 countries or regions
Design	**Clinical Trial -** Randomised, double-blind, placebo-controlled, parallel-group study
Study period	NR
Follow-up duration	12 months
Data source	NA
POPULATION (eligibility)	Outpatients with COPD (GOLD stages III and IV) were recruited based on the following criteria: aged o40 yrs, COPD symptoms for > 2 yrs, smoking history of o10 pack yrs, FEV1/vital capacity (VC) <=70% prebronchodilator, FEV1 <=50% of predicted normal value prebronchodilator, using inhaled bronchodilators as reliever medication, o1 COPD exacerbation requiring a course of oral corticosteroids and/or antibiotics 2–12 months before the first clinic visit. Principal exclusion criteria were: a history of asthma/ seasonal allergic rhinitis before the age of 40 yrs, any relevant cardiovascular disorders or significant disease/disorder, which may have put patients at risk or influenced the results of the study, an exacerbation of COPD requiring medical intervention within 4 weeks prior to enrolment and/or during run-in, use of oxygen therapy, b-blocking agents or non-allowed medications.
POPULATION (baseline participant characteristics)	N= 1022 **Time since diagnosis:** NR **Severity of condition:** mean FEV1 36%, correspond in general to GOLD stages III and IV COPD **Presence of other condition:** **Current smokers:** % 33 39 36 30 Pack-yrs 39 (10–240) 39 (10–150) 38 (10–120) 39 (10–150) **Sex:** Male % 78 74 75 75 **Age years:** 64 (42–86) 64 (41–85) 63 (41–84) 65 (43–85) **Socioeconomic characteristics:** **Other:** **Previous medication % of patients**

	ICS 47 51 48 46
Evaluated ICS	Budesonide
Number of cohorts	N=4 (inhaled budesonide/formoterol (N = 254), budesonide (N = 257), formoterol (N = 255) and placebo (N = 256))
Intervention (ICS)	Inhaled budesonide/formoterol 320/9 mg, budesonide 400 mg
Intervention (Control)	Formoterol 9 mg, placebo
Adjustment method	Treatment and country were used as factors, time in study as an offset variable, and confidence intervals were adjusted for overdispersion.
Included Outcome/s	Pneumonia, Oral Candidiasis, URT, LRTI, HTA, Dysphonia, others

Study ID	**Calverley 2008**
Study acronym	NA
Reference	Calverley, P. M., Rennard, S., Nelson, H. S., Karpel, J. P., Abbate, E. H., Stryszak, P., & Staudinger, H. (2008). One-year treatment with mometasone furoate in chronic obstructive pulmonary disease. Respiratory research, 9(1), 73.
Sponsor	Schering-Plough
Country	Multinational (11 countries)
Objective	To evaluate whether daily PM mometasone furoate administered via a dry powder inhaler (MF-DPI) was equally effective compared to twice daily dosing
Setting	The study was conducted at 95 sites in 11 countries
Design	**Clinical Trial -** Randomized double-blind, placebo-controlled, parallel-group study
Study period	NR
Follow-up duration	52 weeks
Data source	NA
POPULATION (eligibility)	Males and females of any race, ≥ 40 years of age, with a clinical history and spirometry diagnostic of COPD based on currently accepted GOLD criteria, and were current smokers who failed a mandatory smoking cessation program or self-reported ex-smokers who had stopped smoking ≥ 12 months before the study, prebronchodilator FEV1/FVC ratio ≤ 70%, postbronchodilator FEV1 between 30% and 70% predicted, and low postbronchodilator FEV1 reversibility (< 10% of predicted normal). Subjects with a clinical history of asthma or any other clinically significant medical illness other than COPD were excluded. Other

	exclusion criteria included a COPD exacerbation within 3 months before the baseline visit; ventilator support for respiratory failure within the past year; lobectomy, pneumonectomy, or lung volume reduction surgery; lung cancer within the past 5 years; nasal continuous positive airway pressure or oxygen use > 2 L/min or for > 2 hours per day; initiation of pulmonary rehabilitation within the past 3 months; treatment with chronic or prophylactic antibiotics; inability to use the MF-DPI inhaler; and < 80% adherence in recording diary data between screening and baseline.
POPULATION (baseline participant characteristics)	N= 911 **Time since diagnosis:** **Mean COPD duration:** years 7.3 **Severity of condition:** COPD severity, n (%)‡ FEV1 50%–<80% predicted 97 (32) 88 (29) 81 (28) FEV1 30%–<50% predicted 142 (46) 136 (44) 127 (43) FEV1 < 30% predicted 60 (20) 67 (22) 67 (23) Missing§ 8 (3) 17 (6) 20 (7) mean postbronchodilator FEV1 was 1.46 L. **Presence of other condition:** **Mean body mass index:** kg/m2 26.7* 26.1* 27.1 *n = 305 **Sex:** 38% were females and 62% were males **Age:** (Mean age) 65 years **Socioeconomic characteristics:** **Race, n (%):** White 271 (88) 264 (86) 252 (85), Non-white 37 (12) 44 (14) 43 (15)
Evaluated ICS	Mometasone fuorate
Number of cohorts	N=3 (MF-DPI 800 μg QD PM (n = 308), MF-DPI 400 μg BID (n = 308) and Placebo (n = 295))
Intervention (ICS)	MF-DPI 800 μg once daily in the evening and MF-DPI 400 μg twice daily.
Intervention (Control)	Placebo
Adjustment method	NA
Included Outcome/s	Pneumonia, Oral Candidiasis, URTI, others

Study ID	Calverley 2011
Study acronym	INSPIRE
Reference	Calverley, P. M., Stockley, R. A., Seemungal, T. A., Hagan, G., Willits, L. R., Riley, J. H., ... & Investigating New Standards for Prophylaxis in Reduction of Exacerbations (INSPIRE) Investigators. (2011). Reported pneumonia in patients with COPD: findings from the INSPIRE study. Chest, 139(3), 505-512. Wedzicha, J. A., Calverley, P. M., Seemungal, T. A., Hagan, G., Ansari, Z., & Stockley, R. A. (2008). The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. American journal of respiratory and critical care medicine, 177(1), 19-26. Seemungal T, Stockley R, Calverley P, Hagan G, Wedzicha JA. Investigating new standards for prophylaxis in reduction of exacerbations--the INSPIRE study methodology. COPD. 2007;4(3):177-183. doi:10.1080/15412550701407862
Sponsor	GlaxoSmithKline
Country	Multinacional (20 countries)
Objective	To compare the effect of the antiinflammatory/bronchodilator combination of salmeterol/fluticasone propionate (SFC) with the bronchodilator tiotropium bromide on the rate of moderate and/or severe exacerbations during a 2-year treatment period, and secondarily on outcomes that might relate to exacerbations
Setting	NR
Design	**Clinical Trial** - Double-blind, double-dummy parallel study
Study period	2003 -2004
Follow-up duration	2 years
Data source	NA
POPULATION (eligibility)	Patients are aged 40–80 years, with a current or former smoking history of ≥10 pack-years; a history of COPD exacerbations; a post-bronchodilatory forced expiratory volume in one second (FEV1) of less than 50% predicted, reversibility to 400 µg salbutamol 10% or less of predicted FEV_1, and a score of 2 or more on the Modified Medical Research Council dyspnea scale. Exclusion criteria for entry to the run-in period include experience of an exacerbation of COPD in the six weeks before the run-in period, a medical diagnosis of asthma or a respiratory disorder other than COPD, lung transplantation and/or lung volume reduction, and a requirement for regular oxygen therapy. Patients who experience an exacerbation of COPD during the run-in are suspended from the study.

POPULATION (baseline participant characteristics)	N= 1323
	Time since diagnosis: NR
	Severity of condition:
	post-bronchodilator FEV1, 39% predicted
	GOLD stage III (⩾30 to <50% predicted):
	SFC 1.09 (n = 540)
	Tio 1.11 (n = 537)
	GOLD stage IV (<30% predicted):
	SFC0.73 (n = 100)
	Tio 0.71 (n = 101)
	Presence of other condition:
	BMI: kg/m 2 25 (4) 25 (7) 26 (5) 25 (5)
	Current smokers: % 28 50 38 38
	Sex: (male %) 82%
	Age (mean): 64 years
	Socioeconomic characteristics: NR
	Other
Evaluated ICS	Fluticasona
Number of cohorts	N=2 (Salmeterol plus fluticasone propionate (SFC) and Tiotropium bromide (Tio))
Intervention (ICS)	Salmeterol plus fluticasone propionate 50/500 m g bid (SFC) once daily in 2 years
Intervention (Control)	Tiotropium bromide 18 m g once daily (Tio) in 2 years
Adjustment method	NA
Included Outcome/s	Pneumonia, Oral Candidiasis and Eye disorders

Study ID	**Calverley 2007**
Study acronym	**TORCH**
Reference	Calverley, P. M., Anderson, J. A., Celli, B., Ferguson, G. T., Jenkins, C., Jones, P. W., ... & Vestbo, J. (2007). Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. New England Journal of Medicine, 356(8), 775-789.

	Crim, C., Calverley, P. M. A., Anderson, J. A., Celli, B., Ferguson, G. T., Jenkins, C., ... & Vestbo, J. (2009). Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. European Respiratory Journal, 34(3), 641-647. Ferguson, G. T., Calverley, P. M., Anderson, J. A., Jenkins, C. R., Jones, P. W., Willits, L. R., ... & Celli, B. (2009). Prevalence and progression of osteoporosis in patients with COPD: results from the TOwards a Revolution in COPD Health study. Chest, 136(6), 1456-1465. Jenkins, C. R., Jones, P. W., Calverley, P. M., Celli, B., Anderson, J. A., Ferguson, G. T., ... & Vestbo, J. (2009). Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomised, placebo-controlled TORCH study. Respiratory research, 10(1), 59.
Sponsor	GlaxoSmithKline
Country	Multinacional (42 countries)
Objective	To determine if the combination of the long-acting beta-agonist salmeterol and the inhaled corticosteroid fluticasone propionate would reduce mortality among patients with COPD, as compared with usual care
Setting	Outpatients with moderate-to-severe COPD in 444 centers across 42 countries
Design	**Clinical Trial -** Randomized, double-blind trial
Study period	2000-2002
Follow-up duration	3 years
Data source	NA
POPULATION (eligibility)	40 to 80 years of age and had received a diagnosis of COPD, with a prebronchodilator forced expiratory volume in 1 second (FEV1) of less than 60% of the predicted value, an increase of FEV1 with the use of 400 µg of albuterol of less than 10% of the predicted value for that patient, and a ratio of prebronchodilator FEV1 to forced vital capacity (FVC) equal to or less than 0.70.
POPULATION (baseline participant characteristics)	N= 6184 **Time since diagnosis:** NR **Severity of condition:** Mean value of postbronchodilator FEV1 was 44% of the predicted value **Presence of other condition:** **Body-mass index:** 25.4±5.2 25.4±5.2 25.4±5.1 25.4±5.3 **Sex:** (males %) 75% **Age (mean):** 65 y

	Socioeconomic characteristics: Current smoker — no. (%) 658 (43) 651 (43) 661 (43) 660 (43) Pack-years — no. 48.6±26.9 49.3±27.7 49.2±28.6 47.0±26.5 **Other:** Previous treatment — no. (%)‡ Inhaled corticosteroid 338 (22) 273 (18) 306 (20) 292 (19)
Evaluated ICS	Fluticasona
Number of cohorts	N=4 (Placebo Group (N=1524), Salmeterol Group (N=1521), Fluticasone Group (N=1534) and Combination Therapy Group (N=1533))
Intervention (ICS)	combination of salmeterol at a dose of 50 μg and fluticasone propionate at a dose of 500 μg (Advair Diskus, Seretide, GlaxoSmithKline) or salmeterol (Serevent, GlaxoSmith-Kline) alone at a dose of 50 μg, fluticasone propionate (Flovent Diskus, Flixotide, Glaxo-Smith-Kline) alone at a dose of 500 μg, or placebo, all taken in the morning and the evening for 3 years. Study medications were administered as a dry powder with the use of an inhaler (Diskus, Accuhaler, GlaxoSmithKline).
Intervention (Control)	Placebo
Adjustment method	NA
Included Outcome/s	Pneumonia, Oral Candidiasis, URTI, HTA, Fracture, Eye disorders, Dysphonia, Others Adverse events and medications were reviewed at each study visit. Additional information was collected about any fractures, classified as either traumatic or nontraumatic, with nontraumatic fractures considered to be caused by falls from less than standing height or falls occurring spontaneously. Dual-energy x-ray absorptiometry at the hip and lumbar spine and slit-lamp examinations were performed on patients' entry into the study and annually thereafter in a safety substudy conducted in the United States and involving 658 patients. Crim 2009. In a post hoc analysis of the TOwards a Revolution in COPD Health (TORCH) study, we analysed and identified potential risk factors for adverse event reports of pneumonia in this RCT

Study ID	**Calverley 2003b**
Study acronym	**TRISTAN**
Reference	Calverley, P., Pauwels, R., Vestbo, J., Jones, P., Pride, N., Gulsvik, A., ... & Maden, C. (2003). Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. The Lancet, 361(9356), 449-456.
Sponsor	GlaxoSmithKline
Country	Multinacional (25 countries)

Objective	To determine whether long-acting β2 agonists and inhaled corticosteroids in combination will result in treatment effects that are better than those associated with either drug alone in symptomatic chronic obstructive pulmonary disease (COPD)
Setting	Outpatients with COPD from 196 hospitals in 25 countries.
Design	**Clinical Trial** Randomised, double-blind, parallel-group, placebo-controlled study
Study period	NR
Follow-up duration	2-week run-in to the trial, a 52-week treatment period with clinic visits at weeks 0, 2, 4, 8, 16, 24, 32, 40, and 52, and a 2-week post-treatment follow-up
Data source	NA
POPULATION (eligibility)	All patients had a baseline FEV1 before bronchodilation that was 25–70% of that predicted, an increase of less than 10% of predicted FEV1 30 min after inhaling 400 ⬚g salbutamol, and a prebronchodilator FEV1/forced vital capacity (FVC) ratio of 70% or less; history of at least 10 pack-years of smoking (i.e., equivalent to 20 cigarettes smoked per day for 10 years), of chronic bronchitis, at least one episode of acute COPD symptom exacerbation per year in the previous 3 years, and at least one exacerbation in the year immediately before trial entry that required treatment with oral corticosteroids, antibiotics, or both. We excluded patients who had respiratory disorders other than COPD, required regular oxygen treatment, or had received systemic corticosteroids, high doses of inhaled corticosteroids (>1000 µg daily beclometasone dipropionate, budesonide, or flunisolide or >500 µg daily fluticasone), or antibiotics in the 4 weeks before the 2 week run-in period before the trial began.
POPULATION (baseline participant characteristics)	N= 1465 Placebo 361, Salmeterol 372, Fluticasona 374, Combination 358 **Time since diagnosis:** NR **Severity of condition:** Postbronchodilator FEV1 (mL) 1379 (476) 1346 (463) 1363 (460) 1419 (549) **Presence of other condition:** Current smoker: 171 (47 %) 191 (51 %) 198 (53 %) 186 (52 %) Pack-years smoked: 43.4 (22.4) 43.7 (21.9) 41.5 (20.7) 42.0 (22.4) **Sex:** (Male) 269 (75 %) 261 (70 %) 260 (70 %) 270 (75 %) **Age:** 63·4 (8.6) 63.2 (8.6) 63.5 (8.5) 62.7 (8.7) **Socioeconomic characteristics:** NR **Other:** Withdrawal after randomisation 140 (39 %) 119 (32 %) 108 (29 %)* 89 (25 %)†‡

	Previous ICS use 188 (52 %) 183 (49 %) 202 (54 %) 178 (50 %)
Evaluated ICS	Fluticasona
Number of cohorts	N=4 (Placebo (N= 361), Salmeterol (N= 372), Fluticasone (N= 374) and Salmeterol and fluticasone combination (N= 358))
Intervention (ICS)	Salmeterol and fluticasone combination (50/500 μg twice daily) Fluticasone (500 μg twice daily)
Intervention (Control)	Salmeterol (50 μg twice daily), Placebo
Adjustment method	NA
Included Outcome/s	Oral Candidiasis, URTI, LRTI, other

Study ID	**Crim 2015**
Study acronym	NA
Reference	Dransfield, M. T., Bourbeau, J., Jones, P. W., Hanania, N. A., Mahler, D. A., Vestbo, J., ... & Lettis, S. (2013). Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. The Lancet Respiratory Medicine, 1(3), 210-223. DiSantostefano, R. L., Li, H., Hinds, D., Galkin, D. V., & Rubin, D. B. (2014). Risk of pneumonia with inhaled corticosteroid/long-acting β2 agonist therapy in chronic obstructive pulmonary disease: a cluster analysis. International journal of chronic obstructive pulmonary disease, 9, 457. Crim, C., Dransfield, M. T., Bourbeau, J., Jones, P. W., Hanania, N. A., Mahler, D. A., ... & Lettis, S. (2015). Pneumonia risk with inhaled fluticasone furoate and vilanterol compared with vilanterol alone in patients with COPD. Annals of the American Thoracic Society, 12(1), 27-34.
Sponsor	GSK
Country	Multinational
Objective	To determine the incidence of pneumonia, risk factors, and clinical attributes with inhaled fluticasone furoate (FF) in patients with COPD with an exacerbation history.
Setting	Study 1 was at 167 sites in 15 countries and study 2 at 183 sites in 15 countries
Design	**POOLED -** Two replicate multicentre, randomised, double blind, parallel-group studies
Study period	2009-2011
Follow-up duration	52 weeks

Data source	NA
POPULATION (eligibility)	Eligible people were outpatients aged 40 years or older, had a history of COPD as defined by the American Thoracic Society or the European Respira tory Society,18 a smoking history of 10 or more pack-years, a ratio of forced expiratory volume in 1 s (FEV1) to forced vital capacity of 0·70 or less after bronchodilators, an FEV1 after bronchodilators of 70% or less of predicted,19 and a documented history of one or more COPD exacerbations in the year before screening for which they were given systemic or oral corticosteroids or antibiotics or admitted to hospital.
POPULATION (baseline participant characteristics)	N = 3,255 **Time since diagnosis:** NR **Severity of condition:** mean (SD) % predicted post-bronchodilator FEV1 of 45.4% (13.4). **Presence of other condition:** **BMI:** 26.9 (5.9) kg/m2 Forty-four percent of the subjects were current smokers with a mean smoking history of 46.2 (27.7) pack-years. **Sex:** (male) 57.5% **Age:** 63.7 (9.2) **Other**
Evaluated ICS	Fluticasona
Number of cohorts	N=4 (FF/VI (50/25 ug) (n = 820), FF/VI (100/25 ug) (n = 806), FF/VI (200/25 ug) (n = 811) and VI (25 ug) alone (n = 818)) FF: fluticasone furoate VI: vilanterol trifenatate
Intervention (ICS)	3 study groups contained ICS: FF/VI (50, 100, or 200 ug of FF combined with 25 ug of VI), administered once daily ICS = fluticasone furoate
Intervention (Control)	VI 25 ug alone, administered once daily Control: vilanterol trifenatate
Adjustment method	NA
Included Outcome/s	Pneumonia*, LRTI, Fracture, BMD, Eye disorder, Diabetes, other. *Pneumonia as an adverse event (AE) or serious AE (SAE) was defined as described previously (3) and coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 14.1; International Federation of Pharmaceutical Manufacturers *and Associations, Geneva, Switzerland).* There was no a priori definition of pneumonia. Investigators were given guidance on criteria to consider when identifying an AE of pneumonia.

	Nonetheless, the final determination of the AE as pneumonia or exacerbation was made at the investigators' discretion.

Study ID	**Devereux 2019**
Study acronym	**TWICS trial**
Reference	Devereux, G., Cotton, S., Fielding, S., McMeekin, N., Barnes, P. J., Briggs, A., ... & De, S. (2019). Low-dose oral theophylline combined with inhaled corticosteroids for people with chronic obstructive pulmonary disease and high risk of exacerbations: a RCT. Health Technology Assessment.
Sponsor	Health Technology Assessment programme of the National Institute for Health Research.
Country	UK
Objective	To determine the clinical effectiveness and cost-effectiveness of adding low-dose theophylline to a drug regimen containing ICSs in people with COPD at high risk of exacerbation.
Setting	The trial was conducted in 121 UK primary and secondary care sites.
Design	**Clinial Trial –** A multicentre, pragmatic, double-blind, randomised, placebo-controlled clinical trial) (ISRCTN27066620)
Study period	Recruitment to the trial took place between 6 February 2014 and 31 August 2016.
Follow-up duration	1 yest (there were 1489 person-years of follow-up data)
Data source	NA
POPULATION (eligibility)	People >40 yr with COPD [i.e. who have a forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) of < 0.7] currently on a drug regimen including ICSs with a history of two or more exacerbations treated with antibiotics and/or oral corticosteroids (OCSs) in the previous year. The key exclusion criteria are listed below. They include concomitant treatment with drugs with the potential to increase plasma theophylline concentration above the low-dose range of 1–5 mg/l: l severe or unstable ischaemic heart disease l a predominant respiratory disease other than COPD, including alpha-1-antitrypsin deficiency l current use of drugs with the potential to increase plasma theophylline.
POPULATION (baseline participant characteristics)	N = 1578 **Time since diagnosis:** NR

	Severity of condition: mean FEV1 was 51.7% (±20.0%) predicted; mean of 3.6 (±2.2) exacerbations in the previous 12 months; GOLD D 94.7%
	Presence of other condition: 32% smoked
	Sex: (male %) 54%
	Age: The mean age was 68.4 (±8.4) años
	Socioeconomic characteristics: NR
	Other:
Evaluated ICS	ICS (not detailed)
Number of cohorts	N=1
Intervention (ICS)	- ICS only: 2% - ICS/LABA: 16.7% - ICS/LAMA: 1.5% - ICS/LABA/LAMA: 79.9%
Intervention (Control)	NA
Adjustment method	NA
Included Outcome/s	Pneumonia* *Total number of episodes of pneumonia

Study ID	**Doherty 2012**
Study acronym	NA
Reference	Doherty, D. E., Tashkin, D. P., Kerwin, E., Knorr, B. A., Shekar, T., Banerjee, S., & Staudinger, H. (2012). Effects of mometasone furoate/formoterol fumarate fixed-dose combination formulation on chronic obstructive pulmonary disease (COPD): results from a 52-week Phase III trial in subjects with moderate-to-very severe COPD. International journal of chronic obstructive pulmonary disease, 7, 57. Tashkin, D. P., Doherty, D. E., Kerwin, E., Matiz-Bueno, C. E., Knorr, B., Shekar, T., ... & Staudinger, H. (2012). Efficacy and safety of a fixed-dose combination of mometasone furoate and formoterol fumarate in subjects with moderate to very severe COPD: results from a 52-week Phase III trial. International journal of chronic obstructive pulmonary disease, 7, 43. Tashkin, D. P., Doherty, D. E., Kerwin, E., Matiz-Bueno, C. E., Knorr, B., Shekar, T., ... & Staudinger, H. (2012). Efficacy and safety characteristics of mometasone furoate/formoterol fumarate fixed-dose combination in subjects with moderate to very severe COPD: findings from pooled analysis of two randomized, 52-week

	placebo-controlled trials. International journal of chronic obstructive pulmonary disease, 7, 73.
Sponsor	Merck Sharp & Dohme Corp
Country	International
Objective	To assess the clinical efficacy and safety of two doses of MF/F metered dose inhaler (MDI) daily: 400/10 µg BID and 200/10 µg BID versus the individual components or placebo in adult subjects with moderate-to-very severe COPD
Setting	NR
Design	**Clinical Trial (pooled)***
Study period	2007 - 2010
Follow-up duration	52 weeks. The placebo subjects were discontinued from the trial after 6 months, owing to concerns about placebo treatment for a longer period
Data source	NA
POPULATION (eligibility)	Males or females ≥ 40 years old with FEV1/FVC ≤ 0.70, with a post-bronchodilator FEV1 of 25%–60% predicted. Additional inclusion criteria were: symptoms of COPD for at least 24 months prior to enrollment; current or ex-smokers with ≥ 10 pack/year history; no use of parenteral steroids, oral steroids, or antibiotics within 4 weeks prior to screening; and clinically acceptable laboratory tests at screening.
POPULATION (baseline participant characteristics)	N=1196 **Time since diagnosis:** NR **Severity of condition:** FEV /FVC ≤0.70, with a post-bronchodilator FEV of 25%–60% predicted **Presence of other condition:** 32% smoked **Sex:** (male %) 75% **Age:** (mean) 59 years **Socioeconomic characteristics**: NR **Other:**
Number of cohorts	N=5 (MF/F 400/10 µg (n = 225), MF/F 200/10 µg (n = 239), MF 400 µg (n = 253), F 10 µg (n = 243), placebo (n = 236))
Intervention (ICS)	Mometasone furoate/formoterol fumarate (MF/F)
Intervention (Control)	Placebo
Adjustment method	Analysis of covariance (ANCOVA), extracting sources of variation due to treatment, country, smoking status, and baseline
Included Outcome/s	Pneumonia, Osteoporosis (BMD), Hypertension, Upper respiratory tract infection, Influenza, Dysphonia

Study ID	**Ferguson 2008**
Study acronym	**SCO40043**

Reference	Ferguson, G. T., Anzueto, A., Fei, R., Emmett, A., Knobil, K., & Kalberg, C. (2008). Effect of fluticasone propionate/salmeterol (250/50 μg) or salmeterol (50 μg) on COPD exacerbations. Respiratory medicine, 102(8), 1099-1108.
Sponsor	GlaxoSmithKline
Country	USA and Canada
Objective	To evaluate the effect of FSC 250/50 on moderate to severe exacerbations in patients with COPD and who had a history of prior exacerbations.
Setting	94 research sites in the United States and Canada
Design	**Clinical Trial** - Randomized, double-blind, parallel-group study
Study period	NR
Follow-up duration	52 weeks
Data source	NA
POPULATION (eligibility)	Patients were 40 years of age or older with a diagnosis of COPD, a cigarette smoking history of greater than or equal to 10 pack-years, a pre-albuterol FEV1/FVC of 0.70 or less, a FEV1 of 50% of predicted normal or less and a history of 1 or more exacerbations of COPD in the year prior to the study that required treatment with oral corticosteroids, antibiotics, or hospitalization. Patients were excluded if they had a diagnosis of asthma, a significant lung disease other than COPD, a clinically significant and uncontrolled medical disorder including but not limited to cardiovascular, endocrine or metabolic, neurological, psychiatric, hepatic, renal, gastric, and neuromuscular diseases, or had a COPD exacerbation that was not resolved at screening.
POPULATION (baseline participant characteristics)	N = 782 **Time since diagnosis:** NR **Severity of condition:** severe airway obstruction (mean pre-albuterol FEV1 of 32.8% of predicted normal) **Presence of other condition:** **Body mass index:** kg/m2 (FSC 250/50) 27.3 ± 6.2, (Salmeterol) 27.7 ± 7.4 **Current smoker (%):** (FSC 250/50) 40, (Salmeterol) 38 **Smoking history**: [pack-years] (FSC 250/50) 58.5 ± 30.6, (Salmeterol) 54.4 ± 25.7 **Sex:** (Male %): (FSC 250/50) 58, (Salmeterol) 52 **Age:** years 64.9 9.0 65.0 9.1 **Socioeconomic characteristics:** White race 93%

	Other: the majority (56%) were using inhaled corticosteroids or an inhaled corticosteroid/ long-acting beta2-agonist combination at screening.
Evaluated ICS	Fluticasone
Number of cohorts	N=2 (fluticasone propionate/salmeterol (N = 394) and salmeterol (N = 388))
Intervention (ICS)	fluticasone propionate/salmeterol (250/50 mg)
Intervention (Control)	salmeterol (50 mg)
Adjustment method	NA
Included Outcome/s	Pneumonia, Oral Candidiasis, URTI, BMD, Eye disorder and Dysphonia

Study ID	**Johnell 2002**
Study acronym	**EUROSCOP**
Reference	Pauwels, R. A., Löfdahl, C. G., Laitinen, L. A., Schouten, J. P., Postma, D. S., Pride, N. B., & Ohlsson, S. V. (1999). Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. New England Journal of Medicine, 340(25), 1948-1953. Johnell, O., Pauwels, R., Löfdahl, C. G., Laitinen, L. A., Postma, D. S., Pride, N. B., & Ohlsson, S. V. (2002). Bone mineral density in patients with chronic obstructive pulmonary disease treated with budesonide Turbuhaler®. European Respiratory Journal, 19(6), 1058-1063.
Sponsor	Astra- Zeneca Research and Development Lund
Country	Multinacional (9 european countries: Belgium, Denmark, Finland, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom)
Objective	To evaluate the impact of long-term inhaled corticosteroid therapy on bone density and metabolism in a population at risk of osteoporosis.
Setting	Thirty-nine study centres in nine European countries
Design	**Clinical Trial -** randomized, double-blind, placebo-controlled parallel-group study
Study period	1992-1993
Follow-up duration	3 years
Data source	NA
POPULATION (eligibility)	Persons 30 to 65 years of age were eligible if they were currently smoking at least five cigarettes per day and had smoked cigarettes for at least 10 years or had a smoking history of at least 5 pack-

years. The FEV 1 after the use of a bronchodilator had to be between 50 percent and 100 percent of the predicted normal value, and the ratio of prebronchodilator FEV1 to slow vital capacity had to be less than 70 percent. The increase in FEV1 after the inhalation of 1 mg of terbutaline from a dry-powder inhaler had to be less than 10 percent of the predicted normal value.

The change in FEV1 between the end of the first three-month period of the run-in phase and the end of the second had to be less than 15 percent. Subjects with a history of asthma, allergic rhinitis, or allergic eczema and those who had used oral glucocorticoids for more than four weeks during the preceding six months were excluded. The use of inhaled glucocorticoids other than the study medication, beta-blockers, cromones, or long-acting inhaled b2-adrenergic agonists was not allowed.

POPULATION (baseline participant characteristics)	N=912
	Time since diagnosis: NR
	Severity of condition: Prebronchodilator FEV1 (% of predicted) 76.9±13.2 76.8±12.4
	Sex: (males) 73%
	Age (mean): 52 years
	Socioeconomic characteristics: NR
Number of cohorts	N=2 653 (budesonide group, placebo group)
Intervention (ICS)	Budesonide: 400 μg, twice-daily
Intervention (Control)	Placebo from a dry-powder inhaler
Adjustment method	The slopes were calculated for various periods with stratification according to confounders, effect modifiers, or both, and were compared between treatment groups
Included Outcome/s	Vertebral fractures, Osteoporosis (BMD), Oropharyngeal candidiasis (Pauwells 1999)

Study ID	Kerwin_2019
Study acronym	KRONOS
Reference	Kerwin, E. M., Ferguson, G. T., Mo, M., DeAngelis, K., & Dorinsky, P. (2019). Bone and ocular safety of budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler in COPD: a 52-week randomized study. Respiratory research, 20(1), 167.
	Ferguson GT, Rabe KF, Martinez FJ, et al. Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic

	obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial. Lancet Respir Med. 2018;6(10):747–758. doi:10.1016/S2213-2600(18)30327-8. Ichinose, M., Fukushima, Y., Inoue, Y., Hataji, O., Ferguson, G. T., Rabe, K. F., ... & Ballal, S. (2019). Efficacy and safety of budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler formulated using co-suspension delivery technology in Japanese patients with COPD: a subgroup analysis of the KRONOS study. International Journal of Chronic Obstructive Pulmonary Disease, 14, 2979.
Sponsor	AstraZeneca (Pearl)
Country	US
Objective	To evaluate the effects of the triple fixed-dose combination budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler (BGF MDI), formulated using co-suspension delivery technology, on bone mineral density (BMD) and ocular safety in patients with moderate-to very severe chronic obstructive pulmonary disease (COPD).
Setting	A subset of patients from US sites who were initially enrolled in the 24-week KRONOS study (NCT02497001)
Design	**Clinical Trial -** Phase III, multicenter, randomized, double-blind study
Study period	2015 - 2017
Follow-up duration	52 weeks
Data source	NA
POPULATION (eligibility)	Patients were 40– 80 years of age with an established clinical history of COPD, a smoking history of ≥10 pack-years and a post-bronchodilator forced expiratory volume in 1s (FEV1)/ forced vital capacity ratio <0.70 and post-bronchodilator FEV1 <80% and ≥25% predicted normal value. Exclusion criteria comprised severe osteoporosis, a T-score <−2.5 at baseline or inability to achieve an acceptable BMD scan (BMD exclusion criteria); and inability to dilate pupil ≥6mm, intraocular pressure (IOP) ≥21 mmHg (lowest of 3 readings), or an implanted artificial intraocular lens (ophthalmological exclusion criteria).
POPULATION (baseline participant characteristics)	N= 456 **Time since diagnosis:** NR **Severity of condition:** **COPD severity, n (%):** Severe= (BGF MDI 320/18/9.6μg) 86 (44.3), (BGF MDI 320/9.6μg) 37 (42.0), (GFF MDI 18/9.6μg) 65 (37.4)

Very severe= (BGF MDI 320/18/9.6μg) 13 (6.7), (BGF MDI 320/9.6μg) 6 (6.8), (GFF MDI 18/9.6μg) 18 (10.3)

Presence of other condition:

Body mass index: (mean [SD]): (BGF MDI 320/18/9.6μg) 29.0 (7.4), (BGF MDI 320/9.6μg) 29.0 (5.8), (GFF MDI 18/9.6μg) 29.0 (6.5)

Current smoker, n (%) (BGF MDI 320/18/9.6μg) 101 (52.1), (BGF MDI 320/9.6μg) 42 (47.7), (GFF MDI 18/9.6μg) 95 (54.6)

Number of pack-years smoked:(median [range]) (BGF MDI 320/18/9.6μg) 45.0 (11.2–256.0), (BGF MDI 320/9.6μg) 47.3 (14.3–134.0), (GFF MDI 18/9.6μg) 50.0 (10.0–171.0)

Sex: (male %) 53.1%

Age (mean): 62.8 years

Socioeconomic characteristics: Race, n (%)

White (BGF MDI 320/18/9.6μg) 179 (92.3), (BGF MDI 320/9.6μg) 79 (89.8), (GFF MDI 18/9.6μg) 156 (89.7)

Black (BGF MDI 320/18/9.6μg) 13 (6.7), (BGF MDI 320/9.6μg) 9 (10.2), (GFF MDI 18/9.6μg) 17 (9.8)

Other (BGF MDI 320/18/9.6μg) 2 (1.0), (BGF MDI 320/9.6μg) 0, (GFF MDI 18/9.6μg) 1 (0.6)

Other

Evaluated ICS	Budesonide
Number of cohorts	N=3 (Budesonide/glycopyrrolate/formoterol fumarate (N=195) [BGF], Budesonide/formoterol fumarate (N=89) [BFF] and Glycopyrrolate/formoterol fumarate (N=174) [GFF])
Intervention (ICS)	Budesonide/glycopyrrolate/formoterol fumarate by metered dose inhaler 320/18/9.6 μg twice daily for 52 weeks Budesonide/formoterol fumarate 320/9.6 μg twice daily for 52 weeks
Intervention (Control)	Glycopyrrolate/formoterol fumarate 18/9.6 μg twice daily for 52 weeks (active control)
Adjustment method	N/A
Included Outcome/s	Pneumonia, URTI, LRTI, BMD*, Eye disorder**, Dysphonia **Bone mineral density (BMD)** endpoints included the percentage change from baseline in BMD of lumbar spine segments 2–4 (L2–L4) at Week 52 (primary BMD endpoint) **The primary **ophthalmological endpoint** was the change from baseline (assessed during screening in KRONOS) in the lens opacities classification system III (LOCS III) posterior subcapsular cataract (P) at Week 52

Study ID	Lipson 2018
Study acronym	IMPACT
Reference	Lipson, D. A., Barnhart, F., Brealey, N., Brooks, J., Criner, G. J., Day, N. C., ... & Kilbride, S. (2018). Once-daily single-inhaler triple versus dual therapy in patients with COPD. New England Journal of Medicine, 378(18), 1671-1680.
Sponsor	GlaxoSmithKline.
Country	Multinational (37 countries)
Objective	To evaluate the relative benefits and risks of these three regimens in patients with symptomatic COPD and a history of exacerbations.
Setting	NR
Design	**Clinical Trial** - The IMPACT trial was a phase 3, randomized, double-blind, parallel-group, multicenter trial
Study period	2014 -2017
Follow-up duration	52 weeks
Data source	NA
POPULATION (eligibility)	Patients enrolled were 40 years of age or older and had symptomatic COPD (COPD Assessment Test [CAT] score, ≥10; range, 0 to 40, with higher scores indicating more symptoms; minimal clinically important difference, 2 units). Patients had to have either a forced expiratory volume in 1 second (FEV1) that was less than 50% of the predicted normal value and a history of at least one moderate or severe exacerbation in the previous year, or an FEV1 of 50 to 80% of the predicted normal value and at least two moderate exacerbations or one severe exacerbation in the previous year.
POPULATION (baseline participant characteristics)	N= 10355 **Time since diagnosis:** NR **Severity of condition:** Postbronchodilator FEV1 -%of predicted normal value 45.5±14.8. **Presence of other condition:** **Body mass index:** 26.6; **Former smokers**: n=6768 (65%) **Sex:** (Female) n=3485 (34%) **Age (mean):** 65.3±8.3 **Socioeconomic characteristics:** **Other**

Evaluated ICS	fluticasone
Number of cohorts	N=3 (Triple therapy (n = 4151), Fluticasone Furoate-Vilanterol (n = 4134) and Umeclidinium-Vilanterol (n = 2070))
Intervention (ICS)	**Triple therapy**: Once-daily combination of fluticasone furoate (an inhaled glucocorticoid) at a dose of 100 µg, umeclidinium (a LAMA) at a dose of 62.5 µg, and vilanterol (a LABA) at a dose of 25 µg **Fluticasone furoate–vilanterol**: at doses of 100 µg and 25 µg, respectively
Intervention (Control)	Dual bronchodilator umeclidinium–vilanterol at doses of 62.5 µg and 25 µg, respectively
Adjustment method	NA
Included Outcome/s	Pneumonia, LRTI, HTA and Fracture

Study ID	**Mathioudakis 2013**
Study acronym	N/A
Reference	Mathioudakis AG, Amanetopoulou SG, Gialmanidis IP, Chatzimavridou-Grigoriadou V, Siasos G, Evangelopoulou E, Mathioudakis GA. Impact of long-term treatment with low-dose inhaled corticosteroids on the bone mineral density of chronic obstructive pulmonary disease patients: aggravating or beneficial? Respirology. 2013 Jan;18(1):147-53. doi: 10.1111/j.1440-1843.2012.02265.x. PMID: 22985270.
Sponsor	NR
Country	Greece
Objective	To evaluate the impact of the long-term administration of low-dose ICS on the BMD of patients with COPD.
Setting	Respiratory Department of the General Hospital of Nikaia 'St. Panteleimon', Piraeus, Greece
Design	**Clinical Trial** - Randomised
Study period	NR
Follow-up duration	4-year period
Data source	NA
POPULATION (eligibility)	Male ex-smokers patients with confirmed COPD stages II or III who were clinically stable. Clinical stability was defined as no requirement for antibiotics or oral corticosteroid therapy and no change in respiratory symptoms beyond normal day-to-day variation in the preceding month. Furthermore, controls were male volunteers free from respiratory symptoms and other exclusion criteria, with similar age and smoking history with the patients were recruited.

POPULATION (baseline participant characteristics)	N= 251 cases + 313 controls **Time since diagnosis:** NR **Severity of condition:** All the patients had an FEV1/forced vital capacity ratio below 0.7, with FEV1 30% and <80% predicted. All the controls had FEV1/ forced vital capacity ratio over 0.7 during their first visit. **Presence of other condition:** all patients were ex-smokers **BMI (mean):** B 29.6±2.8, E 22.5±2.7, B+E 27.4±2.9, controls 25.1±3.2 **Sex (n Male):** 100% **Age (mean):** B 62.06±6.7, E 62.11±6.5, B+E 62.08±7, Controls 61.7±7.1 **Socioeconomic characteristics:** NR
Evaluated ICS	ICS
Number of cohorts	N=4 (B (n=176), E (n=75), B+E (n=251), Controls (n=313))
Intervention (ICS)	Low-dose inhaled budesonide (two puffs of 160 mcg daily
Intervention (Control)	Long-acting beta-agonists and anticholinergics
Adjustment method	NR
Included Outcome/s	Osteoporosis (BMD)

Study ID	**Papi 2018**
Study acronym	**TRIBUTE**
Reference	Papi, A., Vestbo, J., Fabbri, L., Corradi, M., Prunier, H., Cohuet, G., ... & Scuri, M. (2018). Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. The Lancet, 391(10125), 1076-1084.
Sponsor	Chiesi Farmaceutici.
Country	Multinacional (17 countries)
Objective	To compare BDP/FF/G with IND/GLY in terms of the rate of moderate to severe COPD exacerbations over 52 weeks of treatment.
Setting	187 sites. The sites were a mixture of primary (n=37), secondary (n=104) and tertiary care centres (n=1), and specialised investigation units (n=45).

Design	**Clinical Trial -** Randomised, parallel group, double blind, double dummy, active controlled phase 3b study
Study period	2015 - 2017
Follow-up duration	52 weeks of treatment
Data source	NA
POPULATION (eligibility)	Eligible patients were aged 40 years or older; current or exsmokers; had a diagnosis of COPD, with a ratio of postbronchodilator (salbutamol 400 µg) forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) of less than 0·7, and severe or very severe airflow limitation (FEV1 <50%); had at least one documented moderate or severe COPD exacerbation in the previous 12 months; were symptomatic at screening, with a COPD Assessment Test total score of at least 10; and, for at least 2 months before screening had used an inhaled corticosteroid plus a longacting β2agonist, an inhaled corticosteroid plus a longacting muscarinic antagonist, a longacting β2agonist plus a longacting muscarinic antagonist, or longacting muscarinic antagonist monotherapy, but not triple therapy. Key exclusion criteria were a current diagnosis of asthma with a physicianjudged need for inhaled or oral corti costeroid therapy for this disorder; clinically significant cardiovascular disorders or laboratory abnormalities; and unstable concurrent disease that could have affected efficacy or safety (as judged by the investigator).
POPULATION (baseline participant characteristics)	N= 1532 **Time since first COPD diagnosis**: (years) ((BDP/FF/G) 8.16 (5.76), (IND/GLY) 7.99 (5.64) **Severity of condition:** Proportion of predicted normal FEV1 value‡,§ 36.4 (8.1); <30% 314 (20.49%), ≥30% to <50% 1217 (79.43%) **BMI:** 26.15 (mean) **Current smokers:** 44.58% **Sex:** (Male) 71.8% **Age:** 64.45 (mean)
Evaluated ICS	Beclometasona
Number of cohorts	N=2 (BDP/FF/G (n=764) and IND/GLY (n=768))
Intervention (ICS)	Two inhalations of extrafine BDP/FF/G (87 µg/5 µg/9 µg) twice per day over 52 weeks
Intervention (Control)	One inhalation of IND/GLY (85 µg/43 µg) per day over 52 weeks
Adjustment method	NA

Included Outcome/s	Pneumonia, Oral Candidiasis and HTA

Study ID	**Rennard 2009**
Study acronym	**NA**
Reference	Rennard, S. I., Tashkin, D. P., McElhattan, J., Goldman, M., Ramachandran, S., Martin, U. J., & Silkoff, P. E. (2009). Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease. Drugs, 69(5), 549-565.
Sponsor	AstraZeneca LP
Country	Multinacional
Objective	To assess the long-term efficacy and tolerability of budesonide/formoterol HFA pMDI in patients with moderate to very severe COPD.
Setting	237 sites in the US, Europe and Mexico
Design	**Clinical Trial -** Randomized, double-blind, double-dummy, parallel-group, active- and placebo-controlled, multicentre study
Study period	2005 - 2007
Follow-up duration	12 month
Data source	NA
POPULATION (eligibility)	The inclusion criteria were designed to select a population with moderate to very severe COPD with previous exacerbations (i.e. appropriate candidates for combination ICS/long-acting b2-adrenoceptor agonist [LABA] therapy): age >=40 years, diagnosis of symptomatic COPD for >2 years, >=10 pack-year smoking history, prebronchodilator forced expiratory volume in 1 second (FEV1) of <=50% of predicted normal and prebronchodilator FEV1/forced vital capacity (FVC) of <70%. Patients were to have a Modified Medical Research Council dyspnoea scale score of ‡2 and a history of at least one COPD exacerbation requiring oral corticosteroids or antibacterials within 1–12 months before the first study visit. Additional enrolment criteria were the same as those in a similar 6-month study by Tashkin et al
POPULATION (baseline participant characteristics)	N= Of 1964 randomized patients, 1355 completed the study **Time since diagnosis:** Months since first COPD symptoms [mean] (SD) (BUD/FM pMDI 320/9 µg) 125 (80.6), (BUD/FM pMDI 160/9 µg) 133 (92.1), (FM DPI 9 µg) 135 (87.2), (PL) 127 (84.5) **Severity of condition:** FEV1 (L) at baselinef (prebronchodilator) [mean] (SD) (BUD/FM pMDI 320/9 µg) 1.0 (0.4), (BUD/FM pMDI 160/9 µg) 1.0 (0.4), (FM DPI 9 µg) 1.0 (0.4), (PL) 1.1 (0.4)

	Sex: (Male) [n] (%) (BUD/FM pMDI 320/9 µg) 308 (62.3), (BUD/FM pMDI 160/9 µg) 310 (62.8), (FM DPI 9 µg) 323 (65.3), (PL)314 (65.3) **Age:** [y] mean (SD) range (BUD/FM pMDI 320/9 µg) 63.2 (8.9) 40–83, (BUD/FM pMDI 160/9 µg) 63.6 (9.2) 42–89, (FM DPI 9 µg) 62.9 (9.1) 41–88, (PL) 62.9 (9.2) 40–84 **Socioeconomic characteristics:** **Other:**
Evaluated ICS	Budesonide
Number of cohorts	N=4 (BUD/FM pMDI 320/9 µg bid (n = 494), BUD/FM pMDI 160/9 µg bid (n = 494), FM DPI 9 µg bid (n = 495) and PL (n = 481)) After meeting eligibility criteria, patients entered a 2-week run-in period, during which they received ICS monotherapy if previously stable on ICS (alone or in combination) and ipratropium bromide at a fixed dose if previously receiving anticholinergics.
Intervention (ICS)	BUD/FM pMDI 160/4.5 µg x 2 inhalations bid (320/9 µg), n=494 BUD/FM pMDI 80/4.5 µg x 2 inhalations bid (160/9 µg), n=494
Intervention (Control)	FM DPI 4.5 µg x 2 inhalations bid (9 µg), n=495 PL bid (twice daily), n=481
Adjustment method	NA
Included Outcome/s	Pneumonia, Oral Candidiasis, URTI, LRTI, BMD, Eye disorder, Dysphonia and other ***Pneumonia events** were reported by physicians based on the Medical Dictionary for Regulatory Activities (version 10.0) pneumonia-related preferred terms (pneumonia, bronchopneumonia, lobar pneumonia or pneumonia staphylococcal).

Study ID	Sharafkhaneh 2012
Study acronym	NA
Reference	Sharafkhaneh, A., Southard, J. G., Goldman, M., Uryniak, T., & Martin, U. J. (2012). Effect of budesonide/formoterol pMDI on COPD exacerbations: a double-blind, randomized study. Respiratory medicine, 106(2), 257-268.
Sponsor	AstraZeneca
Country	Multinacional (USA, Central and South America, South Africa)
Objective	Evaluated the effect of budesonide/formoterol pressurized metered-dose inhaler (pMDI) on COPD exacerbations.
Setting	180 study sites in the United States (106 sites), Central and South America (53 sites), and South Africa (21 sites).

Design	**Clinical Trial -** Randomized, double-blind, double-dummy, parallel-group, 12-month multicenter study
Study period	2007 – 2009
Follow-up duration	13 months The study consisted of an initial screening visit (visit 1), a 2- week run-in period (beginning at visit 2), a 12-month randomized treatment period (visits 3 - 9), and telephone follow-up 2 weeks after study treatment cessation.
Data source	NA
POPULATION (eligibility)	Smokers or ex-smokers with a smoking history of ≥10 pack- years. Age: ≥40 years. Clinical diagnosis of COPD with symptoms for >2 year. History of ≥1 COPD exacerbation requiring treatment with a course of systemic corticosteroids, antibiotics, or both, within 1-12 months before screening (visit 1) and documented use of an inhaled short-acting bronchodilator as rescue medication.
POPULATION (baseline participant characteristics)	N= 1219 **Time since diagnosis:** Months since first COPD symptoms, mean (SD) (BUD/FM pMDI 320/9ug)126 (86.7), (BUD/FM pMDI 160/9ug bid) 122 (81.8), (FM DPI 9ug bid) 120 (86.5) **Severity of condition:** 2 Exacerbations in past 1e12 months, n (%) (BUD/FM pMDI 320/9ug)163 (40.0), (BUD/FM pMDI 160/9ug bid) 165 (40.4), (FM DPI 9ug bid)169 (41.9) **Habitual smoker**: n (%) (BUD/FM pMDI 320/9ug)130 (31.9), (BUD/FM pMDI 160/9ug bid) 135 (33.1), (FM DPI 9ug bid)138 (34.2) **Sex (Men):** n (%) (BUD/FM pMDI 320/9ug) 262 (64.4), (BUD/FM pMDI 160/9ug bid) 264 (64.7), (FM DPI 9ug bid)229 (56.8) **Age:** years Mean (SD) (BUD/FM pMDI 320/9ug) 63.8 (9.4), (BUD/FM pMDI 160/9ug bid) 62.8 (9.2), (FM DPI 9ug bid) 62.5 (9.4) **Socioeconomic characteristics:** Race, n (%) White (BUD/FM pMDI 320/9ug) 338 (83.0), (BUD/FM pMDI 160/9ug bid) 332 (81.4), (FM DPI 9ug bid) 332 (82.4); Black (BUD/FM pMDI 320/9ug) 14 (3.4), (BUD/FM pMDI 160/9ug bid) 15 (3.7), (FM DPI 9ug bid)19 (4.7); Asian (BUD/FM pMDI 320/9ug) 7 (1.7) 4 (1.0), (FM DPI 9ug bid) 3 (0.7) Other (BUD/FM pMDI 320/9ug) 48 (11.8) 57 (14.0), (FM DPI 9ug bid) 49 (12.2)
Evaluated ICS	**Budesonide**
Number of cohorts	N=3 (BUD/FM pMDI 320/9ug bid (n=407), BUD/FM pMDI 160/9ug bid (n=408) and FM DPI 9ug bid (n=403))

Intervention (ICS)	Budesonide/formoterol pMDI 160/4.5 mg x 2 inhalations (320/9 mg) twice daily Budesonide/formoterol pMDI 80/4.5 mg x 2 inhalations (160/9 mg) twice daily
Intervention (Control)	Formoterol DPI 4.5 mg x 2 inhalations (9 mg) twice daily
Adjustment method	NA
Included Outcome/s	Pneumonia, URTI, LRTI and HTA

Study ID	Singh 2016
Study acronym	**TRILOGY**
Reference	Singh, D., Papi, A., Corradi, M., Pavlišová, I., Montagna, I., Francisco, C., ... & Vestbo, J. (2016). Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. The Lancet, 388(10048), 963-973.
Sponsor	Chiesi Farmaceutici SpA
Country	Multinacional
Objective	Assessed the efficacy of single-inhaler combination of an extra fine formulation of beclometasone dipropionate, formoterol fumarate, and glycopyrronium bromide (BDP/FF/GB) in COPD compared with beclometasone dipropionate and formoterol fumarate (BDP/FF) treatment.
Setting	159 sites across 14 countries. The sites were a mixture of primary, secondary, and tertiary care providers, and specialist investigation units.
Design	**Clinical Trial -** Randomised, parallel group, double-blind, active-controlled study
Study period	2014 – 2016
Follow-up duration	52 weeks
Data source	NA
POPULATION (eligibility)	The main inclusion criteria were being aged 40 years or older; having a diagnosis of COPD, with a post-bronchodilator forced expiratory volume in 1 s (FEV1) of less than 50% and a ratio of FEV1 to forced vital capacity (FVC) of less than 0·7; at least one moderate or severe COPD exacerbation in the previous 12 months; and the use of an inhaled corticosteroid plus a long-acting β2 agonist (as a free or fixed combination), or an inhaled corticosteroid plus a long-acting muscarinic antagonist, or a long-acting β2 agonist plus a long-acting muscarinic antagonist (as a free or fixed combination), or long-acting muscarinic antagonist

	monotherapy for at least 2 months before screening (patients receiving triple therapy of an inhaled corticosteroid plus a long-acting β2 agonist plus a long acting muscarinic antagonist were not eligible). Additionally, all patients needed to be symptomatic for inclusion, classified as a COPD Assessment Test (CAT) total score of 10 or more and a Baseline Dyspnea Index (BDI) focal score of 10 or less at screening, with the BDI criterion also confirmed at the randomisation visit. The key criteria for exclusion were a diagnosis of asthma, or history of allergic rhinitis or atopy; a COPD exacerbation in the 4 weeks before screening or during the run-in period; clinically significant cardiovascular conditions or laboratory abnormalities; or unstable concurrent disease that might have affected efficacy or safety (as judged by the investigator)
POPULATION (baseline participant characteristics)	N= 1368 **Time since diagnosis:** Time since first COPD diagnosis (years) 7·7 (5·8), (BDP/FF) 7.7 (6.0) **Severity of condition:** FEV1 (L)* 1·11 (0·32) 1·10 (0·33) FEV1 percentage predicted* 36·9 (8·4) 36·2 (8·6) 30% to <50% 532 (77%) 525 (77%) <30% 155 (23%) 155 (23%) FVC (L)* 2·73 (0·76) 2·75 (0·76) FEV1/FVC ratio* 0·42 (0·11) 0·41 (0·11) **BMI (**kg/m2) (BDP/FF/GB) 26·3 (5·4), (BDP/FF)26.4 (5.3) **Current smoker** (BDP/FF/GB) 323 (47%), (BDP/FF) 318 (47%) Patients with at least one concomitant disease‡ (BDP/FF/GB) 590 (86%), (BDP/FF) 563 (83%); Hypertension (BDP/FF/GB) 404 (59%), (BDP/FF) 382 (56%) **Sex:** (Male) (BDP/FF/GB) 509 (74%), (BDP/FF) 527 (77%) **Age (years):** 63.3 (mean) **Socioeconomic characteristics:** Race: White (BDP/FF/GB)684 (100%), (BDP/FF) 679 (100%) **Other:** COPD medication at study entry ICS/LABA 506 (74%) 487 (72%) ICS/LAMA 10 (1%) 10 (1%)
Evaluated ICS	Beclametasona
Number of cohorts	N=2 (BDP/FF/GB (N=687) and BDP/FF (N=680))
Intervention (ICS)	Beclometasone Dipropionate (BDP) 100ug
Intervention (Control)	Formoterol fumarate (FF) 6ug, and glycopyrronium bromide (GB) 12.5 ug (BDP/FF/GB), twice per day via pressurised metered dose inhaler for the 52-week treatment period.
Adjustment method	NA
Included Outcome/s	Pneumonia, Oral Candidiasis and HTA

Study ID	Vestbo 1999
Study acronym	NA
Reference	Vestbo, J., Søorensen, T., Lange, P., Brix, A., Torre, P., & Viskum, K. (1999). Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. The Lancet, 353(9167), 1819-1823.
Sponsor	ASTRA and the National Union against Lung Diseases
Country	Denmark
Objective	To investigate the efficacy of inhaled budesonide on decline in lung function and respiratory symptoms in a 3-year placebo-controlled study of patients with COPD.
Setting	Patients recruited at 1 center
Design	**Clinical Trial** - Parallel-group, randomised, double-blind, placebo-controlled design in a single-centre study, nested in a continuing epidemiological survey (The Copenhagen City Heart Study).
Study period	NR
Follow-up duration	3 years
Data source	NA
POPULATION (eligibility)	Age 30–70 years; no asthma; FEV1/vital capacity ratio 0·7 or less; FEV1 which showed no response (<15% change) to 1 mg inhaled terbutaline or prednisolone 37·5 mg orally once daily for 10 days. Pack-years or other measures of cigarette smoking were not part of inclusion criteria. The main exclusión criterion was long-term treatment (more than two episodes of more than 4 weeks) with oral or inhaled steroids within 6 months of study entry.
POPULATION (baseline participant characteristics)	N= 290 **Time since diagnosis:** NR **Severity of condition:** mean FEV1 2.37 L or 86% of predicted **Presence of other condition:** 76% current smokers. **Sex:** (Male) (BD) 85 (58.6%), (PL) 90 (62.1%) **Age:** (years) (BD) 59.0 (8.3), (PL) 59.1 (9.7) **Socioeconomic characteristics:** NR
Number of cohorts	N=2 (Budesonide (n = 145) and placebo (n = 145))
Intervention (ICS)	Budesonide, 800 ug plus 400 ug daily for 6 months followed by 400 ug twice daily for 30 months
Intervention (Control)	Placebo for 36 months

Adjustment method	NA
Included Outcome/s	Pneumonia

Study ID	**Vestbo 2017**
Study acronym	**TRINITY**
Reference	Vestbo, J., Papi, A., Corradi, M., Blazhko, V., Montagna, I., Francisco, C., ... & Singh, D. (2017). Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial. The Lancet, 389(10082), 1919-1929.
Sponsor	Chiesi Farmaceutici SpA.
Country	Multinational (15 countries)
Objective	We compared treatment with extrafine beclometasone dipropionate, formoterol fumarate, and glycopyrronium bromide (BDP/FF/GB; fixed triple) with tiotropium, and BDP/FF plus tiotropium (open triple).
Setting	COPD outpatients recuited from the participating centers. 224 sites across 15 countries. The sites were a mixture of primary care (17), secondary care (121), tertiary care (48), and specialist investigation units (38).
Design	**Clinical Trial -** Double-blind, parallel-group, randomised, controlled trial (NCT01911364)
Study period	Between Jan 21, 2014, and March 18, 2016
Follow-up duration	52 weeks (aprox 1 year)
Data source	NA
POPULATION (eligibility)	Eligible patients were 40 years of age or older; current or ex-smokers; had a diagnosis of COPD, with post-bronchodilator (salbutamol 400 μg) forced expiratory volume in 1 s (FEV1) of less than 50% and a ratio of FEV1 to forced vital capacity of less than 0·7; had at least one moderate or severe COPD exacerbation in the previous 12 months; and used an inhaled corticosteroid plus long-acting β2-agonist (as an open or fixed combination), or inhaled corticosteroid plus long-acting muscarinic antagonist, or inhaled long-acting β2-agonist plus long-acting muscarinic antagonist (as an open or fixed combination), or long-acting muscarinic antagonist monotherapy for at least 2 months before screening patients receiving triple therapy of inhaled corticosteroid, long-acting β2-agonist and long-acting muscarinic antagonist were not eligible. Additionally, eligible patients were symptomatic, with a COPD Assessment Test total score of at least 10. All patients

	provided written informed consent before any study-related procedure.
POPULATION (baseline participant characteristics)	N= 2691 **Time since first COPD diagnosis (years):** 7·9 (5·6) 8·2 (6·1) 7·8 (5·4) **Severity of condition:** FEV % of predicted: 36·6% (8·3) 36·6% (8·1) 36·7% (8·3); Exacerbation rate in the previous year (range): 1·3 (1–11) 1·3 (1–5) 1·2 (1–7); CAT total score: 21·5 (5·8) 21·6 (5·8) 21·7 (6·0) **BMI (kg/m²):** 26·4 (5·1) 26·2 (4·7) 26·3 (5·3) **Smoking status:** Ex-smoker 560 (52%) 573 (53%) 271 (50%),Current smoker 517 (48%) 503 (47%) 266 (50% **Sex:** (% male) 829 (77%) 830 (77%) 397 (74%) **Age (Mean age):** 63·4 (8·7) 63·3 (8·4) 62·6 (8·9) **Socioeconomic characteristics:** NR
Evaluated ICS	Budesonide
Number of cohorts	N=3 (extrafine beclometasone dipropionate, formoterol fumarate, and glycopyrronium bromide (BDP/FF/GB; fixed triple) (n=1078), Tiotropium (n=1075) and BDP/FF plus tiotropium (open triple) (n=538))
Intervention (ICS)	BDP/FF/GB (fixed triple) Free combination of BDP/FF in one inhaler and tiotropium in a second inhaler (open triple)
Intervention (Control)	Monotherapy long-acting muscarinic antagonist, tiotropium
Adjustment method	NA
Included Outcome/s	Pneumonia, Oral Candidiasis, URTI, LRTI and Dysphonia

Study ID	**Wedzicha 2016**
Study acronym	**FLAME**
Study ID	Wedzicha, J. A., Banerji, D., Chapman, K. R., Vestbo, J., Roche, N., Ayers, R. T., ... & Vogelmeier, C. F. (2016). Indacaterol–glycopyrronium versus salmeterol–fluticasone for COPD. New England Journal of Medicine, 374(23), 2222-2234. Wedzicha, J. A., Zhong, N., Ichinose, M., Humphries, M., Fogel, R., Thach, C., ... & Banerji, D. (2017). Indacaterol/glycopyrronium versus salmeterol/fluticasone in Asian patients with COPD at a high risk of exacerbations: results from the FLAME study. International journal of chronic obstructive pulmonary disease, 12, 339.

Study acronym	Novartis
Reference	Multinacional
Sponsor	To investigate whether the long-acting beta-agonist (LABA) indacaterol plus the long-acting muscarinic antagonist (LAMA) glycopyrronium once daily would be at least as effective as the LABA salmeterol plus the inhaled glucocorticoid fluticasone twice daily in preventing COPD exacerbations
Setting	Patients were enrolled at 356 centers in 43 countries
Design	**Clinical Trial -** Randomized, double-blind, double-dummy, noninferiority trial
Study period	2013 - 2015
Follow-up duration	52 weeks
Data source	NA
POPULATION (eligibility)	Male or female adults aged ≥40 years, with stable COPD according to the current GOLD strategy, current or ex-smokers who have a smoking history of at least 10 pack years; with a post-bronchodilator FEV1 ≥25 and < 60% of the predicted normal value, and post-bronchodilator FEV1/FVC < 0.70 at day -28, a documented history of at least 1 COPD exacerbation in the previous 12 months that required treatment with systemic glucocorticosteroids and/or antibiotics, taking stable COPD medication prior to day 28, and with an mMRC grade of at least 2 at day 28.
POPULATION (baseline participant characteristics)	N= 3362 **Time since diagnosis:** NR **Duration of COPD:** yr 7.3±5.4 **Severity of condition:** Grade EPOC (GOLD); Grupo A+B: 24%, Grupo C+D: 76% **Current smoker** — no. (%) 1333 (39.6) **Sex (n male):** 2557 (76.1) **Age (mean):** 64.6±7.8 **Socioeconomic characteristics:** NR
Evaluated ICS	Fluticasone
Number of cohorts	N=2 (Indacaterol–glycopyrronium and Salmeterol–fluticasone)
Intervention (ICS)	Indacaterol (110 μg) plus glycopyrronium (50 μg) once daily (n = 1680) for 52 weeks
Intervention (Control)	Salmeterol (50 μg) plus fluticasone (500 μg) twice daily for 52 weeks (n = 1682)

Adjustment method	Subgroup analyses, defined according to 15 baseline characteristics
Included Outcome/s	Pneumonia, Oral Candidiasis, URTI and LRTI

Study ID	**Wise 2000**
Study acronym	**LUNG HEALTH STUDY (LHS) II**
Reference	Lung Health Study Research Group. (2000). Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. New England Journal of Medicine, 343(26), 1902-1909. Eichenhorn, M. S., Wise, R. A., Madhok, T. C., Gerald, L. B., Bailey, W. C., Tashkin, D. P., ... & Lung Health Study Research Group. (2003). Lack of long-term adverse adrenal effects from inhaled triamcinolone: Lung Health Study II. Chest, 124(1), 57-62.
Sponsor	National Institutes of Health (NHLBI-5U01-HL50267-05). Triamcinolone and placebo, as well as support for ancillary safety studies, were provided by Rhône–Poulenc Rorer (now Aventis).
Country	USA - Canada
Objective	COPD results from a progressive decline in lung function, which is thought to be the consequence of airway inflammation. We hypothesized that antiinflammatory therapy with inhaled corticosteroids would slow this decline.
Setting	Participants were recruited from among those who had previously participated in or been screened for the Lung Health Study. The Lung Health Study was a trial of smoking cessation and the use of inhaled bronchodilators in 5887 smokers with airflow obstruction, conducted at 10 centers between November 1986 and May 1994.
Design	**Clinical Trial -** Randomized, placebo-controlled clinical trial
Study period	1994-1995
Follow-up duration	4 years
Data source	NA
POPULATION (eligibility)	The participants were 40 to 69 years of age and had airflow obstruction, with a ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) of less than 0.70 and a value for FEV1 that was 30 to 90 percent of the predicted value. All were current smokers or had quit within the previous two years. Candidates were excluded if they had medical conditions such as cancer, recent myocardial infarction, alcoholism, heart failure, insulin-dependent diabetes mellitus, and neuropsychiatric disorders, or if they had used bronchodilators or oral or inhaled corticosteroids in the previous year.

POPULATION (baseline participant characteristics)	N= 1116 **Time since diagnosis:** NR **Severity of condition:** FEV1 % of predicted value: 64.9±13.5 - 63.4±13.2 **Presence of other condition:** Current smoking (%): 90.5 - 89.8, **Cigarettes per day:** 22.9±12.2 - 24.2±13.3 **Sex (% male):** 64 – 62.1 **Age (mean):** 56.2±6.8 - 56.4±6.8 **Socioeconomic characteristics:** Non-white race (% of participants) 6.3 4.1
Evaluated ICS	Triamcinolone
Number of cohorts	N=2 (Inhaled triamcinolone acetonide (N=559) and Placebo (N=557))
Intervention (ICS)	Inhaled triamcinolone acetonide administered at a dose of 600 μg twice daily. Six inhalations twice daily were prescribed, resulting in a dose of 1200 μg per day for the triamcinolone group.
Intervention (Control)	Placebo
Adjustment method	Adjustment for base-line covariates including sex, age, smoking status, base-line lung function, and base-line bronchodilator response.
Included Outcome/s	Oral Candidiasis, BMD, Eye disorders, Diabetes and Adrenal suppression.

Study ID	**Wouters 2005**
Study acronym	**COSMIC**
Reference	Wouters, E. F. M., Postma, D. S., Fokkens, B., Hop, W. C. J., Prins, J., Kuipers, A. F., ... & Creutzberg, E. C. (2005). Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial. Thorax, 60(6), 480-487.
Sponsor	GlaxoSmithKline
Country	Netherlands
Objective	To investigate whether the potentially beneficial effects of the ICS fluticasone propionate on FEV1 remain after long term (1 year) withdrawal of ICS following 3 months run-in treatment with the combination of the LABA salmeterol and fluticasone

Setting	Patients were recruited from 39 centres in the Netherlands (general and academic hospitals) by their chest physician
Design	**Clinical Trial**
Study period	NR
Follow-up duration	12 months
Data source	NA
POPULATION (eligibility)	Inclusion criteria for entry to the study were: male or female patients aged 40–75 years, an established history of COPD, current or ex-smokers with a smoking history of at least 10 pack years, pre-bronchodilator FEV1 30–70% of predicted, FEV1/FVC ratio ,88% for men and ,89% for women, and reversibility ,10% of predicted normal FEV1 after inhaling 400 mg salbutamol. Furthermore, patients had a history of at least two COPD exacerbations in the last year treated with a course of oral corticosteroids and/or antibiotics. Patients were excluded if they had respiratory disorders other than COPD, were using regular oxygen therapy, maintenance systemic corticosteroids, or other investigational drugs in the 4 weeks before entry to the run-in period, had serious uncontrolled (psychological) disease, myocardial infarction, acute heart failure, or angina pectoris in the 3 months before entry to the run-in period, were hypersensitive to one of the study drugs, had evidence of alcohol, drug or solvent abuse, or had previously been enrolled to the present study.
POPULATION (baseline participant characteristics)	N= 373 **Time since diagnosis:** NR **Severity of condition:** Prebronchodilator FEV1, (% predicted)* At start of run-in 49.0 (11.6) 48.1 (11.6) At randomisation 48.2 (12.9) 47.4 (13.9) **Current smoker:** 64 (35%) 74 (39%) Pack-years smoked* 37.8 (18.1) 34.8 (17.4) **Sex (n (%) Male):** 137 (75%) 138 (73%) **Age (mean):** 63 **Socioeconomic characteristics:** NR
Evaluated ICS	Fluticasone
Number of cohorts	N=2 (Salmeterol alone (n = 184) and Salmeterol + fluticasone (n = 189))
Intervention (ICS)	Salmeterol 50 mg + fluticasone 500 mg twice daily (in the morning and evening) via the Diskus inhaler
Intervention (Control)	Salmeterol 50 mg alone
Adjustment method	RmANOVA (age, sex, centre, and smoking status as covariates)

Included Outcome/s	Oral Candidiasis and fracture

COHORT STUDIES

Study ID	**Ajmera 2016**
Study acronym	**NA**
Reference	Ajmera, M., Shen, C., & Sambamoorthi, U. (2017). Concomitant medication use and new-onset diabetes among Medicaid beneficiaries with chronic obstructive pulmonary disease. Population health management, 20(3), 224-232.
Sponsor	NA
Country	US
Objective	The objective was to examine the relationship between the use of antidepressants, ICSs, and statins and new onset diabetes among Medicaid beneficiaries with COPD.
Setting	design using multiple years (2005–2008) of Medicaid claims for beneficiaries with newly diagnosed COPD (n = 15,287), who were diabetes free at baseline.
Design	Retrospective longitudinal cohort
Study period	2005-2008
Follow-up duration	1y
Data source	Medicaid
POPULATION (eligibility)	Medicaid beneficiaries with newly-diagnosed COPD were identified between January 1, 2006 and December 31, 2007. Other inclusion criteria included: (1) no COPD diagnoses during the baseline period; (2) no diabetes diagnoses (ICD-9-CM: 250.x2) during the baseline period; (3) 40–64 years of age (among young adults, this age group is at highest risk of COPD); (4) continuous eligibility during the baseline and follow-up periods; (5) no dual Medicaid/Medicare coverage; (6) enrolled in fee-for-service plans throughout the study observation period; (7) alive during the study

	observation period; and (8) use of services (inpatient or outpatient).
POPULATION (baseline participant characteristics)	N= 6554 **Time since diagnosis:** NR **Severity of condition:** NR **Presence of other condition:** **Other condition** (n=1209) 37.9, (n=641) 20.1, (n=1244) 39.0 **Sex:** (women) n=4209 (47.4%) **Age:** 40-49 (42.1%), 50-59 (42.9%), 60-64 (44.4%) **Socioeconomic characteristics:** white (44.1), afro-american (40.5) **Other**
Evaluated ICS	ICS (no determined)
Number of cohorts	N=1
Intervention (ICS)	any ICS
Intervention (Control)	no ICS
Adjustment method	Multivariable logistic regression was used to examine the relationship between antidepressant, ICS, and statin use and new-onset diabetes after controlling for the comprehensive set of independent variables as described. SAS v 9.3 (SAS Institute, Inc., Cary, NC) was used for the analyses.
Included Outcome/s	Diabetes

Study ID	**Caughey 2013**
Study acronym	NA
Reference	Caughey, G. E., Preiss, A. K., Vitry, A. I., Gilbert, A. L., & Roughead, E. E. (2013). Comorbid diabetes and COPD: impact of corticosteroid use on diabetes complications. Diabetes care, 36(10), 3009-3014.
Sponsor	National Health and Medical Research Council/Australian Research Council Ageing Well Ageing Productively Program

Country	Australia
Objective	To examine the dose-dependent risk of diabetes-related complications associated with corticosteroid use in older patients with diabetes and COPD
Setting	Poblacional. The DVA database contains details of all prescription medicines and medical and allied health services and hospitalizations subsidized by DVA for a treatment population of 290,000 veterans, war widows, and widowers. Over 70% of the population are 70 years of age or older; 54% are male and 9.8% live in residential aged care, and they are dispensed an average of 11 unique medicines annually.
Design	**Retrospective cohort study**
Study period	1 July 2001 to 30 June 2008
Follow-up duration	5 years
Data source	Department of Veterans' Affairs (DVA) health administrative claims database
POPULATION (eligibility)	Subjects were included if they were eligible for all health services subsidized by DVA in the 12 months prior to the date of their first (index) dispensing of an oral antidiabetic medicine. The study included new users of either metformin or sulfonylurea medicines, defined by those who did not have a dispensing of these medicines in the 12 months prior.
	Users of other classes of diabetes medicines (insulin, other oral medications, and combination of metformin) were excluded, as prescription of these medicines at the initiation of diabetes treatment is not recommended as first-line pharmacotherapy and may relate to unusual clinical
	circumstances (16).
POPULATION (baseline participant characteristics)	N = 1077
	Time since diagnosis: NR
	Severity of condition: NR
	Presence of other condition:
	DBT 100% Number of comorbid conditions b (median, IQR) 6 (4–8) 7 (5–9) ,0.001
	Sex: (male %)71%

	Age (mean): 80 y
	Socioeconomic characteristics:
	Socioeconomic index of disadvantage:
	Lowest disadvantage (%) 20.1 20.3
	Medium∕low disadvantage (%) 24.8 22.4
	Medium∕high disadvantage (%) 27.7 30.9
	Highest disadvantage (%) 27.4 26.4
	Other:
	Corticosteroid used (%) 40.1 86.8 ,0.001
	In the 12 months after study entry, corticosteroids were used by 724 (67.2%) of those with diabetes and COPD
Evaluated ICS	ICS (not detailed)
Number of cohorts	N=4 (Diabetes and COPD, non-user of CTC (n = 353); Diabetes and COPD, user of CTC Inhaled only (n = 179); Diabetes and COPD, user of CTC Oral only (n = 337); and Diabetes and COPD, user of CTC Inhaled and oral (n = 208))
Intervention (ICS)	Diabetes and COPD + corticosteroids
	For those who received a corticosteroid, the median corticosteroid dose over the 12-month period was 0.34 DDD/day (IQR 0.11–0.83).
	Inhaled corticosteroid only was received by 24.8%, with a median total dose of 0.08 DDD/day (IQR 0.03–0.13); 46.5% received an oral corticosteroid only, with a median total dose of 0.49 DDD /day (IQR 0.21–0.99); and 28.7% received both an inhaled and oral corticosteroid with a median total dose of 0.64 DDD/day (IQR 0.07–3.04)
Intervention (Control)	Diabetes and COPD, non-user of CTC
Adjustment method	Subhazard ratio (SHR). Covariates included age, sex, socioeconomic status, residential status (community dwelling or aged-care resident), number of comorbid conditions (identified using the pharmaceutical based comorbidity index, Rx-Risk-V, number of prescribers, number of unique medicines (excluding those medicines used to identify patients), number of visits to an endocrinologist, number of visits to a pulmonary specialist, number of hospitalizations for conditions other than diabetes, exposure to corticosteroids in the 12 months prior to study entry, and glycated hemoglobin (HbA1c) testing in the 12 months prior to study entry.
Included Outcome/s	Diabetes

	The study end point was time until first hospitalization for a diabetes-related complication, defined by the ICD-10- AM codes E11 and E13–E14 (15). These include diabetic hyperosmolarity with or without coma, diabetic ketoacidosis with or without coma, diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, diabetic angiopathy, and diabetic arthropathy.

Study ID	**Cho 2017**
Study acronym	NA
Reference	Cho, K. H., Kim, Y. S., Linton, J. A., Nam, C. M., Choi, Y., & Park, E. C. (2017). Effects of inhaled corticosteroids/long-acting agonists in a single inhaler versus inhaled corticosteroids alone on all-cause mortality, pneumonia, and fracture in chronic obstructive pulmonary disease: a nationwide cohort study 2002–2013. Respiratory medicine, 130, 75-84.
Sponsor	The study was conducted without external funding
Country	Korea
Objective	To compare the effect of inhaled corticosteroids (ICS) and long-acting β-agonists (LABAs) in a single inhaler on all-cause mortality, and to identify whether there was a difference in adverse effects, including pneumonia and fractures, of these medications in patients who had been newly diagnosed with COPD
Setting	Poblacional. (The NHIS established cohort data representative of the Korean population)
Design	**Retrospective cohort**
Study period	2002 to 2013
Follow-up duration	The mean follow-up period in the study population was 4.4 ± 3.1 years
Data source	Korean National Health Insurance (KNHI) claims database released by the National Health Insurance Services (NHIS) for the period 2002 to 2013
POPULATION (eligibility)	Individuals with diagnosis of COPD, according to all the following criteria: 1) Age ≥ 40 years, 2) ICD-10 codes for COPD, 3) use of one or more COPD medications at least once per year, and 4) undergoing a pulmonary function test before and at 6 months after an initial COPD claim. Of those patients who were newly diagnosed with

	COPD, only new users of ICS or ICS/LABA in a single inhaler for the period 2004-2013 were included.
	Patients who used ICS or ICS/LABA in the past for other diseases such as asthma were excluded.
POPULATION (baseline participant characteristics)	N= 1995
	Time since diagnosis: COPD and general care Duration of COPD, years (n) <1: 1528; 1-5: 350; >5: 117
	Severity of condition: 807 patients had severe (FEV1 < 50%) disease, while 1188 patients were not severely affected (FEV1 50%)
	Presence of other condition:
	Charlson comorbidity index (n)
	1: 1266; 2: 341; 3: 198; >=4: 190
	Sex: (male n) 1381
	Age: 40-49: 220; 50-59: 385; 60-69: 655; >=70: 735
	Other
Evaluated ICS	fluticasone/salmeterol
	budesonide/formoterol
	beclomethasone/formoterol
Number of cohorts	N=4 (Severe COPD (FEV1%<50) ICSs alone (N = 169); Severe COPD (FEV1%<50) ICS/LABAs (N = 638); Non-severe COPD (FEV1%50) ICSs alone (N = 277); and Non-severe COPD (FEV1%50) ICS/LABAs (N = 911))
Intervention (ICS)	ICS/LABAs
Intervention (Control)	ICCs alone
Adjustment method	Analyses controlled for age, sex, health insurance type, household income, residential area, CCI, disability, duration of COPD, number of hospitalizations due to COPD during the 1st year after diagnosis, number of prescriptions for oral steroids, other COPD medication use in the previous year, ICS alone versus ICS/LABA, pulmonary function level, and disease severity
Included Outcome/s	Pneumonia* and fracture**
	The secondary outcome variables were the first hospitalization for pneumonia (ICD-10 codes, J10-J18) and the first hospitalization for fragility fracture of the spine, pelvis, forearm, or hip (ICD-10 codes,

	S32, S52, and S72), as adverse events associated with the use of ICS or ICS/LABA in a single inhaler.
	* The first hospitalization for pneumomia
	** Fractures/First hospitalization for fragility fracture of the spine, pelvis, forearm, or hip

Study ID	**Crim 2009**
Study acronym	**TORCH**
Reference	Crim C, Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Willits LR, Yates JC, Vestbo J. Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. Eur Respir J. 2009 Sep;34(3):641-7. doi: 10.1183/09031936.00193908. Epub 2009 May 14. PMID: 19443528.
Sponsor	GlaxoSmithKline
Country	Multinacional (42 countries)
Objective	To analysed and identified potential risk factors for adverse event reports of pneumonia in this randomised, double-blind trial.
Setting	Outpatients with moderate-to-severe COPD in 444 centres across 42 countries
Design	**Post hoc analysis of the TOwards a Revolution in COPD Health (TORCH) study**
Study period	2000-2002
Follow-up duration	3 years
Data source	NA
POPULATION (eligibility)	40 to 80 years of age and had received a diagnosis of COPD, with a prebronchodilator forced expiratory volume in 1 second (FEV1) of less than 60% of the predicted value, an increase of FEV1 with the use of 400 μg of albuterol of less than 10% of the predicted value for that patient, and a ratio of prebronchodilator FEV1 to forced vital capacity (FVC) equal to or less than 0.70.
POPULATION (baseline participant characteristics)	N= 6184 **Time since diagnosis:** NR

	Severity of condition: Mean value of postbronchodilator FEV1 was 44% of the predicted value **Presence of other condition:** **Body-mass index:** 25.4±5.2 25.4±5.2 25.4±5.1 25.4±5.3 **Sex:** (males %) 75% **Age (mean):** 65 y **Socioeconomic characteristics:** Current smoker — no. (%) 658 (43) 651 (43) 661 (43) 660 (43) Pack-years — no. 48.6±26.9 49.3±27.7 49.2±28.6 47.0±26.5 **Other:** Previous treatment — no. (%)‡ Inhaled corticosteroid 338 (22) 273 (18) 306 (20) 292 (19)
Evaluated ICS	Fluticasona
Number of cohorts	N=4 (Placebo Group (N=1524), Salmeterol Group (N=1521), Fluticasone Group (N=1534) and Combination Therapy Group (N=1533))
Intervention (ICS)	combination of salmeterol at a dose of 50 μg and fluticasone propionate at a dose of 500 μg (Advair Diskus, Seretide, GlaxoSmithKline) or salmeterol (Serevent, GlaxoSmith-Kline) alone at a dose of 50 μg, fluticasone propionate (Flovent Diskus, Flixotide, Glaxo-Smith-Kline) alone at a dose of 500 μg, or placebo, all taken in the morning and the evening for 3 years. Study medications were administered as a dry powder with the use of an inhaler (Diskus, Accuhaler, GlaxoSmithKline).
Intervention (Control)	Placebo
Adjustment method	NA
Included Outcome/s	Pneumonia, Fractures, Eye disorders, LRTI and Diabetes In a post hoc analysis of the TOwards a Revolution in COPD Health (TORCH) study, we analysed and identified potential risk factors for adverse event reports of pneumonia in this RCT

Study ID	**Dekhuijzen 2016**
Study acronym	**Optimum Patient Care Research Database (OPCRD)**

Reference	Dekhuijzen, P. R., Batsiou, M., Bjermer, L., Bosnic-Anticevich, S., Chrystyn, H., Papi, A., ... & Soriano, J. B. (2016). Incidence of oral thrush in patients with COPD prescribed inhaled corticosteroids: effect of drug, dose, and device. Respiratory medicine, 120, 54-63.
Sponsor	Support from Teva Pharmaceuticals Europe B.V.
Country	UK
Objective	The objective of this study was to investigate the incidence of oral thrush in COPD patients receiving ICS as part of their ICS/LABA combination therapy.
Setting	Poblacional. The OPCRD is a bespoke database with focus on patient-reported outcomes that, at the time of this study, contained anonymous data for over 2.4 million patients from over 550 UK primary care practices across England, Scotland, Wales, and Northern Ireland.
Design	**Retrospective cohort study** Historical, observational, matched cohort study
Study period	NR
Follow-up duration	One year after initiation of therapy.
Data source	UK Optimum Patient Care Research Database The OPCRD is a bespoke database with focus on patient-reported outcomes that, at the time of this study, contained anonymous data for over 2.4 million patients from over 550 UK primary care practices across England, Scotland,Wales, and Northern Ireland.
POPULATION (eligibility)	Patients **initiating** long-acting bronchodilators or FDC ICS/LABA therapy. The index date was defined as the date of first prescription for either a fixed dose combination (FDC) ICS/LABA or LABA or LAMA. Patients eligible for inclusion in the study received a quality outcomes framework (QOF) code for COPD diagnosis, were aged ≥40 years at the index date, had at least 2 years of continuous practice data (1 year of baseline and 1 year of outcome data), and received ≥2 prescriptions of FDC ICS/LABA or long-acting bronchodilator during the outcome period (including prescriptions at the index date). Patients were excluded if in the baseline period they received ≥1 prescription for ICS, ≥1 prescription for both LABA and LAMA, maintenance oral corticosteroid prescription, or if they had a

	diagnostic code for any chronic respiratory disease other tan COPD, asthma, or bronchiectasis.
POPULATION (baseline participant characteristics)	N = 8255 **Time since diagnosis: NR** **Severity of condition:** GOLD grade: A (28.2%), B (21.4%), C (25.2%), D (25.2%) FEV1% predicted: 56.9 (19.2) mMRC score: 0-1 (53.4%), ≥2 (46.6%) COPD exacerbations: 0 (48.8%), 1 (31.4%), 2 (11.4%), ≥3 (8.4%) **Presence of other condition:** **BMI:** 27.1 (±5.8) **Diabetes:** 18.4% **Smoking Status:** current smoker 40.8%, es-smoker 51.6% **Sex:** 57% of patients were male, **Age (mean):** 69 years (SD 10) **Socioeconomic characteristics:** NR Other:
Evaluated ICS	Budesonide, fluticasone and beclometasone
Number of cohorts	N=2 (FDC ICS/LABA (N = 8255) and non-ICS therapy (any longacting bronchodilator) (N= 8255))
Intervention (ICS)	Combination therapy included the following: budesonide/formoterol fumarate dihydrate (BUD/ FOR) administered via a DPI device (Symbicort® Turbohaler®); fluticasone propionate/salmeterol xinafoate (FP/SAL; Seretide®) administered via DPI (Accuhaler®) or pMDI (Evohaler®) device; and beclometasone dipropionate/formoterol fumarate dihydrate (BDP/ FOR; Fostair®) administered via a DPI (NEXThaler®) or pMDI device. Patients prescribed BDP/FOR DPI were not included in the subsequent analyses owing to their low number.
Intervention (Control)	The second cohort included patients who were prescribed non-ICS therapy (any long-acting bronchodilator) at the index date, namely LABA, LAMA or their combination.
Adjustment method	Exact matching

Included Outcome/s	Oral Candidiasis*
	*Incidence of oral thrush was defined as the proportion of patients with a diagnosis of oral thrush and/or prescribed antifungal medication for the treatment of oral thrush within the outcome period (occurring at distinct dates).

Study ID	Flynn 2014
Study acronym	NA
Reference	Flynn, R. W., MacDonald, T. M., Hapca, A., MacKenzie, I. S., & Schembri, S. (2014). Quantifying the real life risk profile of inhaled corticosteroids in COPD by record linkage analysis. Respiratory research, 15(1), 141.
Sponsor	Norvatis
Country	Scotland
Objective	To investigate the association between use of ICS in COPD and development of incident diabetes or worsening of prevalent diabetes, and of other adverse events.
Setting	A record linkage study linking COPD and diabetes datasets with prescription, hospitalisation and mortality data via a unique Community Health Index (CHI) number.
Design	**RETROSPECTIVE COHORT STUDY**
Study period	January 2001 and December 2012
Follow-up duration	At least two years of follow-up time
Data source	From the databases from Tayside Scotland. Data from the Tayside Medicines Monitoring Unit (MEMO) database is held within the Health Informatics Centre (HIC).
	In brief, the MEMO database contains several datasets including all dispensed community prescriptions, hospital discharge data, demographic data and biochemistry results. These data can be linked to disease-specific databases such as TARDIS (Tayside Allergy and Respiratory Disease Information System), DARTS (The Diabetes Audit and Research in Tayside Scotland; now called SCIDC) and other routine clinical data, all of which are linked by a

	Community Health Index (CHI) number that is unique to each patient.
POPULATION (eligibility)	Subjects who registered with TARDIS database between January 2000 and December 2012 and who were 40 years old or over at diagnosis and who have at least two years of follow-up time formed the study cohort. The date of their first diagnosis of COPD (defined as having spirometry showing a FEV1/FVC <0.70) was used as the study entry date. Patients who had a cancer diagnosis prior to the diagnosis of COPD were excluded from the study.
	Patients who developed cancer during the follow up time were censored one year prior to the diagnosis of cancer. For the primary analysis patients with type-1 diabetes were excluded.
POPULATION (baseline participant characteristics)	N= 4305
	Time since diagnosis: NR
	Severity of condition:
	Dyspnoea score (1 = least breathless, 5 = most breathless) 2.57 2.19
	FEV1 baseline (Litres) 1.63 (0.65) 1.82 (0.63)
	Presence of other condition:
	BMI (mean): (kg/m2) 26.5
	Smoking (pack years): 35.8
	Sex: (men %) 48.69%
	Age (mean): 65.92 years
	Socioeconomic characteristics:
	Social deprivation (Scottish index of multiple deprivation; 1 = most deprived, 5 = most affluent) 2.31 2.29
	Other:
Evaluated ICS	ICS (not detailed)
Number of cohorts	N=2 (ICS exposed (n = 3243) and ICS un-exposed (n = 1062))
Intervention (ICS)	3,243 were exposed to ICS for a total of 17,229 person- years of exposure,
Intervention (Control)	1,062 patients were unexposed to ICS with a follow-up of 4,508 person-years
Adjustment method	NA

Included Outcome/s	Pneumonia, Fracture, Eye disorder and Diabetes.
	Primary outcomes: (i) Newly diagnosed diabetes – new diagnosis of type 2 diabetes was recognised using the DARTS database, this has 95% sensitivity for identifying people with diabetes. (ii) Worsening of existing diabetic control – defined as either worsening of HbA1c by >5 mmol/mol or the prescription of additional hypoglycaemic agents, following the index visit.
	Secondary endpoints: hospitalisations coded as pneumonia, fractures and cataracts were obtained from SMR1.

Study ID	Gershon 2014
Study acronym	NA
Reference	Gershon, A. S., Campitelli, M. A., Croxford, R., Stanbrook, M. B., To, T., Upshur, R., ... & Stukel, T. A. (2014). Combination long-acting β-agonists and inhaled corticosteroids compared with long-acting β-agonists alone in older adults with chronic obstructive pulmonary disease. Jama, 312(11), 1114-1121
Sponsor	Physicians' Services Incorporated Foundation; Canadian Institutes of Health Research Institute of Nutrition, Metabolism and Diabetes; and University of Toronto
Country	Canada
Objective	To examine the association of LABA-ICS combination therapy compared with LABAs alone and the composite outcome of mortality and COPD hospitalizations in older COPD patients with naturally occurring comorbidities, including asthma, in real world conditions
Setting	Ontario residents aged 66 years or older using multiple linked population health care databases
Design	**Retrospective cohort study -** Population-based, longitudinal cohort study
Study period	2003 to 2011
Follow-up duration	Mean 2.6 years
Data source	- The Ontario Registered Persons Database

	- The Ontario Drug Benefits database
	- The Canadian Institute of Health Information'sDischarge Abstract Database and National Ambulatory CareReporting System
	- The OntarioHealth Insurance Plan physician claims database
POPULATION (eligibility)	All Ontario residents aged 66 years or older who met a validated case definition of physician-diagnosed COPD using health administrative data, and were new users of LABAs or LABA-ICS combination therapy. Individuals who received prescriptions for both medications on the index date, patients who were ineligible for health insurance, and those who had had lung volume reduction surgery or transplantation were excluded.
POPULATION (baseline participant characteristics)	N= 11872 **Time since diagnosis:** 55% more than 5 years **Severity of condition:** NR **Presence of other condition:** HTA 72%, Diabetes 28%; Asthma 28%; cancer other than lung cancer 24% **Sex:** (men %) 53% **Age (mean):** 76 years **Socioeconomic characteristics:** Rural residence 1553 (17.8) 524 (16.6)
Evaluated ICS	ICS (not detailed)
Number of cohorts	N=2 (LABA and ICS (N = 8712) and LABAs alone (N = 3160))
Intervention (ICS)	LABAs and ICSs
Intervention (Control)	LABAs alone
Adjustment method	Propensity score matching. Multivariable logistic regression was used to compute the propensity score for receiving LABAs alone using all the measured baseline characteristics as predictors. Individuals prescribed LABAs were then matched with up to 3 individuals prescribed LABAs and ICSs on the basis of age (±1 year), sex, codiagnosis of asthma, COPD duration, and propensity score.
Included Outcome/s	**Primary outcomes:** pneumònia* and fracture**

Secondary outcomes: hospitalization for pneumonia (ICD-10 codes J10-J18 and J44.0) and hospitalization for fragility fractures of the spine, pelvis, forearm, or hip (ICD-10 codes S32, S52, and S72) likely to result from osteoporosis— both are suggested adverse effects of ICSs.

* Hospitalization for pneumònia

** Hospitalization for fragility fractures of the spine, pelvis, forearm, or hip

Study ID	Gonnelli 2010
Study acronym	**EOLO**
Reference	Gonnelli S, Caffarelli C, Maggi S, Guglielmi G, Siviero P, Rossi S, Crepaldi G, Nuti R; EOLO study group. Effect of inhaled glucocorticoids and beta (2) agonists on vertebral fracture risk in COPD patients: the EOLO study. Calcif Tissue Int. 2010 Aug;87(2):137-43. doi: 10.1007/s00223-010-9392-x. Epub 2010 Jun 22. PMID: 20567964.
Sponsor	NR
Country	Italy
Objective	To evaluate whether the dose of inhaled GCs and b2 agonists may independently influence bone status and vertebral fracture risk in COPD patients aged 50 years or over.
Setting	It was carried out in 57 Italian outpatient pneumological centres. The centres were located in both academic and non-academic general hospitals equipped with facilities for the diagnosis of osteoporosis
Design	**Retrospective cohort study -** Population-based, longitudinal cohort study
Study period	Between January and December 2005
Follow-up duration	NR
Data source	From outpatient pneumological centres
POPULATION (eligibility)	Patients were included if they had a forced expiratory volume of 1 second (FEV1)/forced vital capacity (FVC) ratio \70%, no changes in COPD treatment during the previous 2 months, and a lateral chest X-ray taken at the moment of the inclusion visit or during the preceding 2 months. Patients were excluded if their chest X-ray was prompted by physical trauma or if they had known or suspected malignancy,

	severe hepatic or renal disease, marked scoliosis, or moderate–severe cognitive impairment.
POPULATION (baseline participant characteristics)	N= A total of 3,030 eligible COPD patients, 1,768 men and 1,262 women **Time since diagnosis:** NR **Severity of condition:** COPD severity: Severe (inhaled ICs ≤750 μg) 24.7, (750< inhaled ICs ≤1500 μg) 28.0, (inhaled GCs >1500μg) 28.3 **Presence of other condition:** **Smoking status:** Nonsmokers (%) (inhaled ICs ≤750 μg) 32.7, (750< inhaled ICs ≤1500 μg) 28.7, (inhaled GCs >1500μg) 27.4 **Age (mean):** (inhaled ICs ≤750 μg) 69.9 ± 8.5 years, (750< inhaled ICs ≤1500 μg) 70.8 ± 8.0 years, (inhaled GCs >1500μg) 70.4 ± 7.9 years **Socioeconomic characteristics:** NR **Other:**
Evaluated ICS	ICS (not detailed)
Number of cohorts	N=3 (No treatment, inhaled GCs, other treatment)
Intervention (ICS)	68.5% were treated with glucocorticoids (55.1% inhaled GCs, 3.9% oral GCs, and 9.5% oral+inhaled GCs)
Intervention (Control)	16.7% were not treated with specific COPD medications, and the remaining 14.8% were treated with short- or long-acting b2 agonists, xanthines, and antimuscarinics but not with GCs.
Adjustment method	NR
Included Outcome/s	Fractures

Study ID	Janson 2013
Study acronym	PATHOS
Reference	Janson, C., Larsson, K., Lisspers, K. H., Ställberg, B., Stratelis, G., Goike, H., ... & Johansson, G. (2013). Pneumonia and pneumonia related mortality in patients with COPD treated with fixed combinations of inhaled corticosteroid and long acting β2 agonist: observational matched cohort study (PATHOS). Bmj, 346, f3306.

Sponsor	AstraZeneca
Country	Sweden
Objective	To investigate the occurrence of pneumonia and pneumonia related events in patients with COPD treated with two different fixed combinations of inhaled corticosteroid/long acting β2 agonist
Setting	Primary care medical records data linked to Swedish hospital, drug, and cause of death registry data, for years 1999-2009
Design	**Retrospective cohort study** Observational retrospective pairwise cohort study matched (1:1) for propensity score.
Study period	1999-2009
Follow-up duration	3 years on average
Data source	The study linked primary care medical records to data from national mandatory Swedish registries. Data were collected from the National Patient Register. Drug prescription data were collected from the Swedish Prescribed Drug Register
POPULATION (eligibility)	All male and female patients of any age with COPD diagnosed by a physician (ICD-10 code J44, according to the 2011 ICD-10-CM). Patients eligible for matching were receiving fixed combinations of inhaled corticosteroid/long acting β2 agonist (budesonide/formoterol or fluticasone/salmeterol). No predefined exclusion criteria were included in the protocol.
POPULATION (baseline participant characteristics)	N= 5468 **Time since diagnosis:** NR **Severity of condition:** Post-bronchodilator FEV1 , % predicted normal* 50.4 (19.3) 51.3 (20.2) Presence of other condition: No (%) current smokers 341 (48) 397 (49) Asthma 1052 (38) 1069 (39) Diabetes 288 (11) 283 (10) **Sex:** (females n(%)) 1456 (53) 1446 (53)

	Age: 67.6 (10.4) 67.6 (10.9)
	Socioeconomic characteristics: NR
	Other
Evaluated ICS	Budesonide
	Fluticasone
Number of cohorts	N=2 (Fluticasone/salmeterol (n=2734) and Budesonide/formoterol (n=2734))
Intervention (ICS)	Fluticasone/salmeterol and Budesonide/formoterol
Intervention (Control)	NA
Adjustment method	Pairwise 1:1 propensity score matching. Patients treated with either treatment combination were matched on the following criteria during the two years before index and at index: age; sex; available lung function measurements; number of prescriptions for antibiotics, oral steroids, tiotropium, ipratropium, inhaled corticosteroids, short acting β2 agonists, long acting β2 agonists, angiotensin receptor blockers, β blockers, statins, calcium antagonists, and thiazides; diagnosis of diabetes, asthma, cancer, rheumatoid arthritis, heart failure, hypertension, and stroke; and number of previous admissions to hospital.
	Sensitivity analyses; analysis of rates of pneumonia and mortality from pneumonia in the crude (unmatched) populations
	In dose-response analyses of inhaled corticosteroid dose, the inhaled combination was stratified by collected mean daily steroid dose
Included Outcome/s	Pneumonia

Study ID	**Janson 2018**
Study acronym	**ARCTIC**
Reference	Janson, C., Johansson, G., Ställberg, B., Lisspers, K., Olsson, P., Keininger, D. L., ... & Larsson, K. (2018). Identifying the associated risks of pneumonia in COPD patients: ARCTIC an observational study. Respiratory research, 19(1), 172.
Sponsor	Medical writing support was funded by Novartis Pharma AG (Basel, Switzerland).

Country	Sweden
Objective	to generate evidence to better manage patients with COPD, to foster early diagnosis, and to characterize treatment patterns and associated outcomes.
Setting	52 Swedish primary care centers
Design	**Restrospective cohort study -** Retrospective observational cohort study of longitudinal patient-level data
Study period	2000-2014
Follow-up duration	4 years
Data source	Medical records (EMRs) and registries using an established software system (Pygargus Customized eXraction Program, CXP 3.0) EMR data were linked by the Swedish National Board of Health and Welfare using individual patient identification (ID) numbers to National Registry data sources (patient IDs were pseudonymized): (i) the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA [21]), which includes socio-demographic data including educational level, marital status and family situation, occupational status, retirement, economic compensation and social benefits; (ii) the National Patient Register [22], which contains data relating to diagnosis (ICD-10 code and associated position), surgery, gender, age, region, hospital visits, specialty visits, hospital admissions and discharges, and medical procedures and surgeries performed in the inpatient and outpatient specialist settings; (iii) the National Prescription register [22], which tracks full details of all dispensed medications (ATC codes), including brand name, prescription date, dose, strength, pack size, specialty of the prescriber and costs associated with the drug prescription; and (iv) the Cause of Death Register [22], which holds information on social security number, home district, sex, date of death and cause of death.
POPULATION (eligibility)	Patients eligible for inclusion were those aged ≥40 years with lung function measurements and who had received a doctor's diagnosis of COPD (ICD-10 code: J44), and/or asthma (ICD-10 code: J45/J46) in the primary care setting (EMR database) between the years 2000–2014. The first patient to receive a COPD diagnosis was in 2000 (index date).
POPULATION (baseline participant characteristics)	N= 6623 **Time since diagnosis:** NR **Severity of condition:** NR Presence of other condition:

	Charlson Comorbidity Index value, mean ± SD 1.55 ± 0.8
	Sex: (Female) n (%) 3688 (55.7)
	Age: (mean years ± SD) 65.9 ± 10.1
	Socioeconomic characteristics: NR
	Other:
	ICS use, n (%) No ICS 3385 (51.1) NA Low dose ICSb 2189 (33.0) NA High dose ICSc 1049 (15.8) NA
	Low dose ICS: < 640 µg/day; c High dose ICS: ≥800 µg/day
Evaluated ICS	Budesonide, Fluticasone and ICS (not determined)
Number of cohorts	N=3 (No ICS (n = 3385), Low ICS (n = 2189) and High ICS (n = 1049))
Intervention (ICS)	Low dose ICS: < 640 µg/day High dose ICS: ≥800 µg/day] <u>Types of ICS:</u> Budesonide (71.5%), Fluticasone propionate(7.3%), Budesonide/fluticasone propionate (20.2%) and Other (0.9%)
Intervention (Control)	No ICS group
Adjustment method	Hazard ratio ncluding FEV1 and comorbidities in a multivariate model
Included Outcome/s	Pneumonia

Study ID	Kenderska 2019
Study acronym	N/A
Reference	Kendzerska, T., Aaron, S. D., To, T., Licskai, C., Stanbrook, M., Vozoris, N. T., ... & Gershon, A. S. (2019). Effectiveness and safety of inhaled corticosteroids in older individuals with chronic obstructive pulmonary disease and/or asthma. A population study. *Annals of the American Thoracic Society*, *16*(10), 1252-1262.
Sponsor	Health Systems Research Fund Capacity Grant, Government of Ontario, and Canadian Respiratory Research Network (CRRN).
Country	Canada

Objective	To compare the effectiveness and safety of ICS in older adults with asthma, COPD or features of both in a real-word setting.
Setting	Population based study provincial health administrative data from over two million individuals aged 65 and older living in Ontario, Canada
Design	**Retrospective longitudinal population cohort study**
Study period	2003 - 2014
Follow-up duration	>1 year
Data source	NA
POPULATION (eligibility)	We included all insured Ontario residents aged 66 years and older who met a validated casedefinition of physician-diagnosed COPD (COPD cohort) health administrative data between September 1, 2003, and March 31, 2014 and who received a medication for their disease after being identified. We required people to be at least 66 years to have a one-year look-back period to obtain information on medications use (24). Physician diagnosed COPD was identified using a validated case definition of one or more COPD hospitalizations and/or three or more COPD ambulatory care visits within two years (95.4% specificity [92.6, 97.4] and 57.5% sensitivity [95%CI: 47.9, 66.8]) (26).
POPULATION (baseline participant characteristics)	N= 150593 **Time since diagnosis:** NR **Severity of condition:** NR **Presence of other condition:** 25% with concurrent asthma **Sex:** (men %) 52% **Age (median):** 76 years **Socioeconomic characteristics:** **Other**
Evaluated ICS	NR
Number of cohorts	N=2 (new ICS users (N=47557) and non-ICS users(controls) (N=103036))

Intervention (ICS)	ICS
Intervention (Control)	Non ICS
Adjustment method	Propensity score weighting
Included Outcome/s	Pneumonia, Fracture, Eye disorder and Diabetes.

Study ID	**Kern 2015**
Study acronym	NA
Reference	Kern, D. M., Davis, J., Williams, S. A., Tunceli, O., Wu, B., Hollis, S., ... & Trudo, F. (2015). Comparative effectiveness of budesonide/formoterol combination and fluticasone/salmeterol combination among chronic obstructive pulmonary disease patients new to controller treatment: a US administrative claims database study. Respiratory research, 16(1), 52. Davis, J. R., Kern, D. M., Williams, S. A., Tunceli, O., Wu, B., Hollis, S., ... & Trudo, F. (2016). Health care utilization and costs after initiating budesonide/formoterol combination or fluticasone/salmeterol combination among COPD patients new to ICS/LABA treatment. Journal of managed care & specialty pharmacy, 22(3), 293-304.
Sponsor	AstraZeneca
Country	USA
Objective	To compare the real-world effectiveness of BFC and FSC treatments among COPD patients new to ICS/LABA combination therapy in a population of US managed care enrollees
Setting	Poblacional At the time of this study, the HIRE contained longitudinal claims data of more than 31 million enrollees from all US census regions.
Design	**Retrospective cohort study** Patients were matched 1-to-1 on demographic and pre-initiation clinical characteristics using propensity scores from a random forest model.
Study period	Between 03/01/2009 and 03/31/2012
Follow-up duration	12 months
Data source	Health Core Integrated Research Environment (HIRE)
POPULATION (eligibility)	Patients were required to be naïve to ICS/LABA therapy one year prior to initiating BFC (160/4.5 µg) or FSC (250/ 50 µg), where the pharmacy claim date of treatment initiation during the intake period was considered the index date. Patients were required to be at least 40 years old at the index date, and have at least 12 months of continuous health plan enrollment, prior to (pre-index period)

| | and following the index date (post-index period). Diagnosis criteria required for inclusion were at least one inpatient visit with a primary diagnosis for COPD, and/or, at least, one ED visit with a COPD diagnosis, and/or, at least, two other medical claims with a COPD diagnosis (either primary or secondary) during the pre-index period.

Patients diagnosed with cancer and those who received ≥180 days of oral corticosteroid (OCS) therapy during the 12-month preindex period, and those initiating both study medications on the same date were excluded from the study. |
| --- | --- |
| **POPULATION (baseline participant characteristics)** | N= 7394

Matched patients were well balanced on age (mean = 64 years), gender (BFC: 52% female; FSC: 54%), prior COPD-related medication use, healthcare utilization, and comorbid conditions

Time since diagnosis: NR

Severity of condition:

Prior COPD inpatient visits (mean, SD) 0.13 0.40 0.15 0.42 0.13 0.40 0.14 0.43

Presence of other condition:

Prior asthma diagnosis (n, %) 1371 36.2% 2078 32.3% <0.0001 1320 35.7% 1280 34.6% 0.3299

Sex: (female %) 53%

Age (mean): 64 years

Socioeconomic characteristics: |
| **Evaluated ICS** | Budesonide and fluticasone |
| **Number of cohorts** | N=2 (BFC (N = 3697) and FSC (N = 3697)) |
| **Intervention (ICS)** | budesonide/formoterol combination (BFC)

BFC: 160/4.5 µg

fluticasone/salmeterol combination (FSC)

FSC: 250/50 µg |
| **Intervention (Control)** | NA |
| **Adjustment method** | Propensity score matching was used to adjust for confounders measured pre-index (age, gender, prior asthma diagnosis, and preindex characteristics including COPD-related inpatient hospitalizations and ED visits, OCS fills, antibiotic fills, SABA and/or SABA/SAMA fills, LABA fills, and LAMA fills) |
| **Included Outcome/s** | Pneumonia*

*The outcome of pneumonia (defined as having a claim with a primary or secondary diagnosis with the following diagnosis codes: ICD-9-CM 480.xx –486.xx) was examined in three different ways betweenthe two cohorts. First, the pneumonia rate within each cohort was calculated as the proportion of COPD patients with at least one pneumonia diagnosis during the 12 month post-index follow-up. Second, the time to first pneumonia diagnosis was analyzed to account for possible differences in timing of the |

	diagnoses found in the first analysis. Lastly, pneumonia-related utilization was examined by each place of service: inpatient, ED, and outpatient visit.

Study ID	**Kim 2013**
Study acronym	**NA**
Reference	Kim, J. H., Park, J. S., Kim, K. H., Jeong, H. C., Kim, E. K., & Lee, J. H. (2013). Inhaled corticosteroid is associated with an increased risk of TB in patients with COPD. Chest, 143(4), 1018-1024.
Sponsor	No funding was received for this study
Country	South Korea
Objective	To assess the risk of pulmonary TB among ICS users, based on the presence of the radiologic sequelae of pulmonary TB
Setting	university hospital in Seongnam, South Korea.
Design	**Retrospective cohort study**
Study period	January 1, 2000, to December 31, 2005, and then reviewed their medical records to December 31, 2010
Follow-up duration	5 years
Data source	NR
POPULATION (eligibility)	patients with COPD only patients without active TB were included. In addition, we excluded those who had received a systemic steroid mount of . 7.5 mg of prednisone, or for a duration of . 1 month. Patients who received chemotherapy agents for malignant neoplasm and single-visit patients were also excluded.
POPULATION (baseline participant characteristics)	N= 616 **Time since diagnosis:** NR **Severity of condition:** FEV 1, % predicted 62.5 24.1

	Presence of other condition:
	BMI: kg/m 2 22.4 (3.5)
	Diabetes mellitus: 13.8%
	Current or ex-smoker: 90.4%
	Sex: (male%) 86.9%
	Age: y 65.4 (10.9)
	Socioeconomic characteristics: NR
	Other
Evaluated ICS	budesonide, fl uticasone, ciclesonide, and beclomethasone, whether used alone or in combination with an inhaled b -agonist
Number of cohorts	N=4 (ICS With TB Scar (n = 139); ICS Without TB Scar (n = 170); No ICS With TB Scar (n = 114); and No ICS Without TB Scar (n = 193))
Intervention (ICS)	ICS With TB Scar (n = 139) ICS Without TB Scar (n = 170)
Intervention (Control)	No ICS
Adjustment method	Cox proportional hazard model
Included Outcome/s	Tuberculosis* *Diagnosis of TB Using the chart review, two pulmonologists independently identified patients who developed TB when they met any of the following criteria: positive culture for Mycobacterium tuberculosis; positive acid-fast bacilli smears, TB-polymerase chain reaction (TB-PCR), or interferon g release assay with radiologic change suggesting pulmonary TB; newly developed lymphocyte-dominant pleural effusion with an adenosine deaminase level . 40 IU/L; improvement of radiologic findings after taking anti-TB medications under clinicopathologic diagnosis; or biopsy-proven granuloma with caseous necrosis with/without TB-PCR. Patients with nontuberculous Mycobacterium disease and extrapulmonary TB other than TB pleurisy were excluded.

Study ID	**Lee 2015**
Study acronym	**NA**

Reference	Lee, M. C., Lee, C. H., Chien, S. C., Chang, J. H., She, H. L., Wang, J. Y., & Yu, M. C. (2015). Inhaled corticosteroids increase the risk of pneumonia in patients with chronic obstructive pulmonary disease: a nationwide cohort study. Medicine, 94(42).
Sponsor	NR
Country	Taiwan
Objective	to identify the risk factors of pneumonia among COPD patients identified in the LHID 2005, with special emphasis on the impact of ICS.
Setting	Population based study
Design	**Prospective cohort study**
Study period	2005-2007
Follow-up duration	NR
Data source	The Longitudinal Health Insurance Database (LHID) 2005, a subset database of the NHI program, contains the entire original claims data from 1996 to 2007 of 1,000,000 beneficiaries randomly sampled from the year 2005 Registry for Beneficiaries. National Health Insurance (NHI) of Taiwan database
POPULATION (eligibility)	Patients in the COPD cohort who continuously used ICS for more than 360 days were identified (ICS cohort), in which continuous use was defined as no interruption for more than 30 days.
POPULATION (baseline participant characteristics)	N= 842 **Time since diagnosis:** NR **Severity of condition:** NR **Presence of other condition:** diabetes mellitus (19.0%) malignancy (3.7%) **Sex:** (male %) 74.3% **Age:** 65.9 12.4 years

	Socioeconomic characteristics: Other
Evaluated ICS	budesonide
Number of cohorts	N=2 (COPD cohort (N=6034) and ICS cohort (N=842))
Intervention (ICS)	NA
Intervention (Control)	NA
Adjustment method	NA
Included Outcome/s	Pneumonia* *The diagnostic criteria of pneumonia consisted of a compatible diagnosis (ICD-9-CMcodes 480–486 and A-codesA321) in the out-patient or in-patient discharge records, and prescriptions of pneumonia-specific antibiotics and chest radiography. Pneumonia-specific antibiotics included systemic beta-lactams and/or beta-lactamase inhibitors, fluoroquinolones, macrolides, and carbapenems. The presence of pneumonia events between the enrolment and index dates were also recorded

Study ID	**Lin 2013**
Study acronym	NA
Reference	Lin, S. H., Ji, B. C., Shih, Y. M., Chen, C. H., Chan, P. C., Chang, Y. J., ... & Lin, C. H. (2013). Comorbid pulmonary disease and risk of community-acquired pneumonia in COPD patients. The International journal of tuberculosis and lung disease, 17(12), 1638-1644.
Sponsor	NR
Country	Taiwan
Objective	To evaluate factors associated with CAP occurrence in COPD patients by comparing subjects with and without comorbid pulmonary diseases (lung cancer, bronchiectasis and history of active TB)
Setting	Out-patients newly diagnosed with COPD at Changhua Christian Hospital

Design	Retrospective cohort study
Study period	2006 - 2010
Follow-up duration	1 year
Data source	Out-patient electronic medical records at Changhua Christian Hospital at Taiwan.
POPULATION (eligibility)	We screened all out-patients newly diagnosed with COPD at Changhua Christian Hospital, Changhua City, Taiwan, between 1 January 2006 and 31 December 2010. Out-patient electronic medical records were screened for COPD as defined in Code 496 of the International Classifi- cation of Diseases, Ninth Revision, Clinical Modifi- cation (ICD-9-CM). Patients with any of the following were excluded: no pulmonary function test (PFT) results, PFT results not indicative of COPD (post-bronchodilator, forced expiratory volume in 1 second [FEV_1]/forced vital capacity [FVC] $\geqslant 0.70$) or concurrent asthma.
POPULATION (baseline participant characteristics)	N = 2630 **Time since diagnostic:** NR **Severity of condition:** FEV_1, l 1.68 [1.18–2.30] 1.44 [0.93–1.93] **Presence of other condition:** 370 (14.1%) had comorbid pulmonary disease. **Sex:** (Male n %) 1758 (78.9) 338 (84.1) **Age:** years 70.1 [58.9–78.1] 77.3 [68.6–82.6] **Other**
Evaluated ICS	fluticasone salmeterol budesonide/formoterol
Number of cohorts	N=2 (Community-adquired pneumonia (n=402) and group control with COPD but without CAP (n=2228))
Intervention (ICS)	N= 1002 (38.9%) of 2630 took ICS ICS combined with LABA (fluticasone/ salmeterol or budesonide/formoterol), ICS combined with LABA plus LAMA (tiotropium), or LAMA alone.

	[It is not specified in the study the number/percentage of each medication]
Intervention (Control)	N=1628 (61.90%) of 2630 did not take ICS.
Adjustment method	Cox's proportional hazards regression models were used to calculate crude and adjusted hazard ratios (aHRs).
Included Outcome/s	Pneumonia

Study ID	**Lin 2016**
Study acronym	N/A
Reference	Lin, S. H., Perng, D. W., Chen, C. P., Chai, W. H., Yeh, C. S., Kor, C. T., ... & Lin, C. H. (2016). Increased risk of community-acquired pneumonia in COPD patients with comorbid cardiovascular disease. International Journal of Chronic Obstructive Pulmonary Disease, 11, 3051.
Sponsor	NR
Country	Taiwan
Objective	To assess whether COPD patients with CVD have an increased risk of developing CAP. To assess the use of ICSs to examine the risk of developing CAP in COPD patients.
Setting	Hospitalized COPD patients with CAP
Design	**Retrospective cohort study**
Study period	Patients with newly diagnosed COPD between January 1, 2007 and December 31, 2010 were reviewed.
Follow-up duration	The enrolled patients were followed for at least 3 years.
Data source	As per Lin 2013
POPULATION (eligibility)	Patients with newly diagnosed COPD (ICD-9: 496) between January 1, 2007 and December 31, 2010 were reviewed. COPD was diagnosed according to the GOLD guidelines.

	Patients who had no pulmonary function data or who had history of asthma were excluded.
POPULATION (baseline participant characteristics)	N= 2,440 patients included in the analysis **Time since diagnosis:** NR **Severity of condition:** COPD stage: -Stage I. Mild: n=890 (36.47%) -Stage II. Moderate: n=997 (40.86%) -Stage III. Severe: n=437 (17.90%) -Stage IV. Very severe: n=116 (4.75%) **Sex:** (male) n=1931 (79.13%) **Age (median):** (no CAP)=69.1 (57.9-77.2), (CAP)=77.4 (69.0-82.5); **Socioeconomic characteristics:** NR **Other**
Evaluated ICS	NR
Number of cohorts	N=2 (group with cardiovascular disease and group without cardiovascular disease. We will be using though the following two groups (ICS vs no ICS))
Intervention (ICS)	N=903 (37%)
Intervention (Control)	N=1537 (62.99%)
Adjustment method	Cox's proportional hazards regression model was used to determine the adjusted hazard ratios with 95% confidence intervals in relation to factors associated with CAP in COPD patients with and without CVD.
Included Outcome/s	Pneumonia

Study ID	**Liu 2016**
Study acronym	NA
Reference	Liu, S. F., Kuo, H. C., Liu, G. H., Ho, S. C., Chang, H. C., Huang, H. T., ... & Lin, M. C. (2016). Inhaled corticosteroids can reduce

	osteoporosis in female patients with COPD. International journal of chronic obstructive pulmonary disease, 11, 1607.
Sponsor	This study was supported by a grant from the National Science Council, Taiwan (NSC 102-2314-B-182-053-MY3) and a grant from the Chang Gung Memorial Hospital (CMRPG8C1081 and CMRPG8B0211).
Country	Taiwan
Objective	To assess the incidence of osteoporosis in patients with COPD with ICS use and without.
Setting	The NHI Program, which provides compulsory universal health insurance, was implemented on March 1, 1995, in Taiwan. Under the NHI, 98% of the island's population receives all forms of health-care services including outpatient services, inpatient care, Chinese medicine, dental care, childbirth services, physical therapy, preventive health care, home care, and rehabilitation for chronic mental illness.
Design	**Retrospective cohort study** This is a retrospective cohort and population-based study in which we extracted newly diagnosed female patients with COPD between 1997 and 2009 from Taiwan's National Health Insurance (TNHI) database between 1996 and 2011 (International Classification of Diseases, Ninth Revision – Clinical Modification [ICD-9-CM] 491, 492, 496)
Study period	1996-2011
Follow-up duration	All the study participants were followed from the index date to end point occurrence, withdrawal from the database, or the end of 2011, whichever date came first.
Data source	Taiwan's National Health Insurance (TNHI) database
POPULATION (eligibility)	For the cohort, it was identified an exposed study cohort from the database consisting of newly diagnosed female patients with COPD (n=25,404, ICD-9-CM 491, 492, 496) from 1996 to 2011. Patients were excluded if they were younger than 40 years or if osteoporosis had been diagnosed prior to the diagnosis of COPD and cases of asthma (ICD-9 CM code 493.X) before the index date.
POPULATION (baseline participant characteristics)	N= 10723 **Time since diagnostic:** NR

	Severity of condition: NR
	Presence of other condition:
	Tuberculosis 6.15%, bacterial pneumonia 6.19%, bronchiectasis 8.23%, pumonary fibrosis 0.83%, hypertension 65.69% and diabetes mellitus 36.65%.
	Sex: (women %) 100%
	Age: [≥40 to <50] 20.04%, [≥50 to <60] 20.60% and [≥60] 59.36%.
	Socioeconomic characteristics:
	5,997 patients (55.93%) had an income of 15,840 New Taiwan Dollars (NTD)
	Other
Evaluated ICS	fluticasone propionate budesonide
Number of cohorts	N=2 (ICS users (n=812) and nonusers (n=9,911))
Intervention (ICS)	ICS users Any ICS use (n = 812) >.0 mg to <=20 mg (n = 358) >.20 mg to <=60 mg (n = 208) >.60 mg (n = 246)
Intervention (Control)	Non ICS users (n = 9,911)
Adjustment method	Adjusted for age, income, and use of medications (estrogen, oral steroid, laBa, laMa, and saBa).
Included Outcome/s	BMD (osteoporosis)* *During the study it was identified the end point as the first diagnosis of osteoporosis from outpatient claims or hospitalization records from 1997 to 2011. All the study participants were followed from the index date to end point occurrence, withdrawal from the database, or the end of 2011, whichever date came first.

Study ID	**Morros 2018**

Study acronym	**PNEUMOCORT**
Reference	Morros, R., Vedia, C., Giner-Soriano, M., Casellas, A., Amado, E., & Baena, J. M. (2019). Neumonías adquiridas en la comunidad en pacientes con enfermedad pulmonar obstructiva crónica tratados con corticoides inhalados u otros broncodilatadores. Estudio PNEUMOCORT. Atención Primaria, 51(6), 333-340.
Sponsor	Instituto de Salud Carlos III (EC10-081)
Country	Spain
Objective	To analyze the risk of pneumonia and / or exacerbations in patients with chronic obstructive pulmonary disease (COPD) treated with inhaled corticosteroids (IC) and not treated with IC (NCI). Estimate the risk of pneumonia according to the dose of IC.
Setting	Patients treated at the Primary Care Centers (CAP) of the Catalan Health Institute (ICS)
Design	**Retrospective cohort study**
Study period	2007 - 2011
Follow-up duration	2000 days
Data source	Information System for the Development of Research in Primary Care (SIDIAP)
POPULATION (eligibility)	Older than 45 years, diagnosed with COPD during 2007-2009, with a history of smoking, and with a spirometry performed ± 1 year after diagnosis. Patients with exacerbations in the 6 months prior to inclusion, treated with immunosuppressants, diagnosed with asthma, dementia, transplanted or institutionalized were excluded.
POPULATION (baseline participant characteristics)	N = 3837 **Time since diagnosis:** NR **Severity of condition:** Mild COPD 22.5%, moderate 28.6%, severe 26.3% and very severe 22.5% **Presence of other condition:** 48.1% were smokers **Sex:** (% males) 87.2% males **Age (average age):** 65 years **Other**
Evaluated ICS	Beclometasona, Budesonide and Fluticasone

Number of cohorts	N=2 (ICS (n=2224 (58,0%) and NO ICS (n=1613 (42,0%))
Intervention (ICS)	ICS cohort: 2.224 ● Beclometasona 7,2% ● Budesonida 58,0% ● Fluticasona propionato 36,4%
Intervention (Control)	No ICS cohort: 1.613
Adjustment method	Hazard ratio (HR) adjusted for sex, age, concomitant pathologies, smoking and alcohol habits, baseline respiratory treatment and other treatments, history of exacerbations, pneumonia, and severity of COPD.
Included Outcome/s	Pneumonia

Study ID	**Price 2016**
Study acronym	NA
Reference	Price, D. B., Russell, R., Mares, R., Burden, A., Skinner, D., Mikkelsen, H., ... & Stephens, J. W. (2016). Metabolic effects associated with ICS in patients with COPD and comorbid type 2 diabetes: a historical matched cohort study. PloS one, 11(9).
Sponsor	Boehringer Ingelheim
Country	UK
Objective	To investigate whether ICS therapy in patients with COPD and comorbid type 2 diabetes mellitus (T2DM) has a negative impact on diabetic control, and whether these negative effects are dose-dependent.
Setting	Primary Care (patients in the community)
Design	**Retrospective cohort study** (historical matched cohort study utilising primary care medical record data from two large UK databases)
Study period	2008-2012

Follow-up duration	12 – 18 months
Data source	The Clinical Practice Research Datalink (CPRD) contains de-identified longitudinal data from more than 680 subscribing practices, is well validated and frequently used for medical and health research.[19] The Optimum Patient Care Research Database (OPCRD) is a quality-controlled and respiratory-focused research database containing anonymous, longitudinal data for over two million patients from over 500 UK practices.
POPULATION (eligibility)	Eligible patients (40 years old at the index date) had a spirometry-test validated Quality and Outcomes Framework (QOF) coded diagnosis of COPD at any time (ratio of forced expiratory volume in 1 second to forced vital capacity [FEV1/FVC] <0.7), and a QOF-coded diagnosis of T2DM before the index date. The code lists used for COPD and T2DM can be found in Supplementary methods (S1 File). The QOF is the UK National Health Service pay-for-performance scheme that provides an incentive for practices to deliver better patient care and includes the creation of high-quality electronic disease registers[21, 22], and is known to have improved diabetes care.[23] Patients had to have at least 1 full year of data available during the baseline period, including HbA1c data available at least once within the baseline period, as well as at least once between 20 days and 18 months in the outcome period. The 20-day limit was chosen on the basis that HbA1c levels have been reported to plateau 20 days after intensification of glucose lowering therapy and remain comparable for a further 100 days,[24, 25] while the 18 month limit was designed to capture all valid HbA1c readings, assuming HbA1c values were recorded at least every 15 months as per QOF diabetes indicators specified for the study period.[22] For the ICS cohort, patients were included if they had a first prescription for ICS between 2008 and 2012, with a medication possession ratio for ICS of 50% in the outcome period.[22] For the non-ICS cohort, patients were included if they had a first or additional prescription for non-ICS therapy between 2008 and 2012, and no ICS therapy prior to an HbA1c reading in the outcome period. Exclusion criteria included any record of type 1 diabetes and any prescriptions for maintenance oral corticosteroids in the year before the index date.
POPULATION (baseline participant characteristics)	N = 1364 **Time since diagnosis:** NR **Severity of condition:** ICS Gold A (n=257), Gold B (n=186), Gold C (n=126), Gold D (n=109) FEV1 50-79%, 61% No ICS Gold A (n=256), Gold B (n=187), Gold C (n=127), Gold D (n=108) FEV1 50-79%, 62.5%

	Presence of other condition: Smoking status, n (%)‡ Non-smoker 141 (10.4) 265 (10.1) 31 (4.5) 31 (4.5) Current smoker 414 (30.6) 882 (33.7) 194 (28.4) 194 (28.4) Ex-smoker 800 (59.0) 1473 (56.2) 457 (67.0) 457 (67.0) **BMI**: n (%) Underweight 10 (0.7) 18 (0.7) 0 (0) 0 (0) Normal weight 215 (15.9) 394 (15) 67 (9.8) 67 (9.8) Overweight 428 (31.7) 813 (30.9) 222 (32.6) 222 (32.6) Obese 698 (51.7) 1409 (53.5) 393 (57.6) 393 (57.6) **Sex:** (male %) 73% **Age (mean):** 70.4 ± 9.3 años **Socioeconomic characteristics:** NR **Other**
Evaluated ICS	Fluticasone
Number of cohorts	N=2 (ICS (n = 682) and non-ICS (n = 682)*)
Intervention (ICS)	ICS (Fluticasona)
Intervention (Control)	Non-ICS *Includes prescriptions for SABA, SAMA, LABA, LAMA or their combinations.
Adjustment method	-By the number of acute cycles of oral corticosteroids and Dg of pneumonia between the onset and terms of HbA1c results (*) -By gastroesophageal reflux (**) -For baseline HbAc1 and duration of DM2 (***)
Included Outcome/s	Diabetes* *Study endpoints: • Primary endpoint Change in HbA1c from baseline to outcome period • Secondary endpoints Increase in HbA1c* and/or the addition of antidiabetic medication from baseline to outcome period Number of patients off the QOF target for HbA1c (HbA1c >7.5%) Change in diabetes-related GP visits, hospitalisations, and glucose strip prescriptions† Progression of ongoing diabetes treatment to insulin by time or dose

Study ID	**Price 2019**
Study acronym	NA
Reference	Price, D. B., Voorham, J., Brusselle, G., Clemens, A., Kostikas, K., Stephens, J. W., ... & Fogel, R. (2019). Inhaled corticosteroids in COPD and onset of type 2 diabetes and osteoporosis: matched cohort study. NPJ primary care respiratory medicine, 29(1), 1-13.
Sponsor	Novartis
Country	UK
Objective	To evaluate whether ICS therapy for patients with COPD is associated with an increased onset or accelerated progression of type 2 diabetes mellitus, or with an increased onset of osteoporosis.
Setting	Atención Primaria (pacientes en la comunidad)
Design	**Retrospective cohort study** (matched cohort study) This matched cohort study used two large UK databases (1983–2016) to study patients (≥ 40 years old) initiating ICS or long-acting bronchodilator (LABD) for COPD from 1990–2015 in three study cohorts designed to assess the relation between ICS treatment and (1) diabetes onset (N = 17,970), (2) diabetes progression (N = 804), and (3) osteoporosis onset (N = 19,898).
Study period	1990 - 2015
Follow-up duration	2 years
Data source	Clinical Practice Research Datalink (CPRD) The CPRD contains medical record data for about five million patients from over 600 subscribing practices and has long been used for pharmaco epidemiological research. Optimum Patient Care Research Database (OPCRD) The OPCRD is a database developed to improve patient outcomes through medical research and services, with focus on patient-reported outcomes, that, at the time of this study, contained anonymous data for over 2.4 million patients from over 576 primary care practices across the United Kingdom.

POPULATION (eligibility)	Eligible patients had a record of physician-diagnosed COPD, were aged 40 years or older when prescribed their first ICS or LABD maintenance therapy for COPD, and had continuous medical records for a ≥ 1-year baseline period before the index date (first COPD maintenance therapy), followed by an outcome period of ≥ 2 years.
	The diabetes onset cohort included patients with no prior recorded type 2 diabetes mellitus diagnosis and/or antidiabetic treatment, and not more than one HbA1c reading of > 6.5%, ever before the index date or within 1.5 years after the index date. A prior diagnosis of type 1 diabetes mellitus ever before the index date was also cause for exclusion.
	The diabetes progression cohort included patients with recorded diagnosis and/or treatment for type 2 diabetes mellitus and/or two or more HbA1c readings > 6.5% ever before the index date. In addition, included patients had one or more HbA1c recorded readings in both the baseline year and the outcome period starting at 1.5 years after the index date. The osteoporosis onset cohort included patients with no prior recorded osteoporosis diagnosis ever before the index date or within 1.5 years after the index date.
POPULATION (baseline participant characteristics)	N= 28,060 (ICS) and 9862 (LABD) patients, respectively, were eligible for the study
	Time since diagnosis: NR
	Severity of condition:
	half of patients in each study cohort had experienced one or more moderate-to severe exacerbations in the baseline year, and in each ICS treatment group in the three study cohorts, 60% or 61% of patients in the 2011 GOLD A/B groups were prescribed ICS
	Presence of other condition:
	Body mass index: kg/m2 , mean (SD) 26.5 (5.4) 26.3 (5.3)
	Patients in the diabetes progression cohort included a slightly higher percentage of men (59%, 66%, and 62%, respectively)
	Age: mean ages of the matched treatment groups were 68, 71, and 68 years in diabetes onset, diabetes progression, and osteoporosis onset cohorts
	Socioeconomic characteristics: NR
	Other
Evaluated ICS	ICS (not detailed)
Number of cohorts	N=2 (ICS group and LABD group)

Intervention (ICS)	Patients initiating ICS (the ICS group) had no previous prescriptions for LABA, LAMA, or combination LABA/LAMA and had received two or more ICS prescriptions during at least 2 outcome years. Prescribing of LABD was permitted in the ICS group, and the prescribed ICS drug and/or inhaler could change during the outcome period; the study observation period ended if ICS were stopped. Patients in the ICS and LABD groups were unique, i.e., patients did not contribute data to both cohorts
Intervention (Control)	Patients initiating LABD therapy as LABA, LAMA, or combination LABA/LAMA (LABD group) had no previous ICS prescriptions; the LABD drug(s) could change during outcome, and the study observation period ended if ICS were prescribed.
Adjustment method	Propensity Score The following variables (±their caliper) were used for matching: 1. Year of index date ± 2 years 2. Age ± 5 years 3. Sex 4. Smoking status 5. BMI category (except diabetes progression cohort) 6. Number of exacerbations (recorded as Read code) in the baseline year, categorized
Included Outcome/s	BMD and Diabetes

Study ID	Saeed 2020
Study acronym	NA
Reference	Saeed MI, Eklöf J, Achir I, et al. Use of inhaled corticosteroids and the risk of developing type 2 diabetes in patients with chronic obstructive pulmonary disease [published online ahead of print, 2020 Apr 1]. Diabetes Obes Metab. 2020;10.1111/dom.14040. doi:10.1111/dom.14040
Sponsor	The Research Council of Herlev and Gentofte Hospital
Country	Denmark

Objective	To determine the risk of type 2 diabetes onset associated with accumulated ICS use during the previous year in a population of patients with COPD.
Setting	Hospital outpatient clinic
Design	**Retrospective cohort study** Nationwide observational cohort study
Study period	2010 -2017
Follow-up duration	7 years (until death or a T2D event)
Data source	The Danish Register of Chronic Obstructive Pulmonary Disease (DrCOPD), the Danish National Patient Register (DNPR), the Danish National Health Service Prescription Database (DNHSPD)
POPULATION (eligibility)	All Danish patients with COPD who were registered at an outpatient clinic visit in DrCOPD -Edad: ≥ 40 años
POPULATION (baseline participant characteristics)	N= 33466 propensity-matched population -time since diagnosis NR -severity of condition FEV1% predicted, median (IQR) 49 (37-62) -presence of other condition Body mass index (kg/m2), median (IQR) 25 (21-28) Hypertension, n (%) 4,506 (26.9%) 4,548 (27.2%) -sex Male, n (%) 7,722 (46.1%) 7,696 (46.0%) -age Age, median (IQR) 72 (64-79) 72 (65-79) -socioeconomic characteristics NR -other
Evaluated ICS	Exposure was defined as use of ICS, assessed via ICS prescriptions, 365 days before study entry to 14 days after in order to include the

	respiratory physician's prescription at the first outpatient clinic visit. The doses from the ICS prescriptions were converted into budesonide equivalent doses and were accumulated throughout the year. Thereafter, mean daily doses were calculated and divided into four exposure groups: no ICS use; 0 µg, low; 0-369.99 µg, medium; 370-969.99 µg and high; ≥970 µg daily. We did not register prescriptions during the follow-up period in the main analysis, as adverse effects from glucocorticoids can occur after discontinued use [17] and to ensure that ICS exposure was before onset of T2D.
Number of cohorts	N=4 (No ICS use, Low ICS use, Medium use and High use)
Intervention (ICS)	- Low ICS use: 0-369.99 µg daily - Medium use: 370-969.99 µg daily - High use: ≥ 970 µg daily
Intervention (Control)	No ICS use: 0 µg
Adjustment method	A propensity-matched Cox model and an adjusted Cox proportional hazards model (stratified on body mass index (BMI)) were used to estimate the hazard ratio (HR) for new-onset T2D.
Included Outcome/s	Diabetes The outcome of interest was new onset of T2D. To identify persons with new onset of T2D, an extraction algorithm from The Danish Health Data Authority was used: a T2D event was defined as a primary or secondary diagnosis of T2D (ICD10 E11 and sub-codes) in the DNPR and/or at least two filled prescriptions for antidiabetic drugs excluding insulin and insulin analogues (ATC code A10B) in the DNHSPD (Figure 1). The date of T2D event was defined as the date of T2D diagnosis or the date of the second prescription for antidiabetic drugs, whichever came first. Patients with previous diabetes diagnosis (ICD10 E10-14) and/or polycystic ovary syndrome (ICD10 E28.2) were excluded from our study. In addition, patients using growth hormone products (ATC code H01AC), certain antipsychotics (the top three causing hyperglycaemia [18]: chlorpromazine ATC code N05AA01, olanzapine ATC code N05AH03, clozapine ATC code N05AH02) and topical steroids from prescriptions (ATC code D07A) up to a year before study entry were also excluded from our study. The mortality date was specified in the DrCOPD.

Study ID	**Shu 2010**
Study acronym	NA

Reference	Shu CC, Wu HD, Yu MC, Wang JT, Lee CH, Wang HC, Wang JY, Lee LN, Yu CJ, Yang PC; Taiwan Anti-Mycobacteria Investigation (TAMI) Group. Use of high-dose inhaled corticosteroids is associated with pulmonary tuberculosis in patients with chronic obstructive pulmonary disease. Medicine (Baltimore). 2010 Jan;89(1):53-61. doi: 10.1097/MD.0b013e3181cafcd3. PMID: 20075705.
Sponsor	NR
Country	Taiwan
Objective	To evaluate the influence of ICS on the risk of pulmonary TB in patients with COPD.
Setting	Tertiary-care referral center in northern Taiwan
Design	**Retrospective cohort study**
Study period	August 2000 and July 2008
Follow-up duration	At least a mean of 41.8 months
Data source	Pharmacy Department of National Taiwan University Hospital for providing the records of patients_ medication.
POPULATION (eligibility)	We identified all patients aged more than 40 years who had irreversible airflow limitation between August 2000 and July 2008. The irreversible airflow limitation was defined as 1) ratio of FEV1 to forced vital capacity (FVC) e0.70,21 and 2) a reversibility of G12% and G200 mL from prebronchodilator FEV1 to FEV1 after 200 Kg albuterol inhalation.2,21 Among these patients, only those who had been followed in our hospital for 93 months were included for further analysis. Patients who had chronic lung disease other than COPD were excluded.
POPULATION (baseline participant characteristics)	N= 554 **Time since diagnosis:** NR **Severity of condition:** FEV1 (mL) (mean): (HD) 1249 ±514, (MD) 1503±597, (LD) 1549±583, (no ICS) 1776±630 **Presence of other condition:** **Sex:** (male n (%)) (HD) 31 (62), (MD) 54 (75), (LD) 113 (58), (no ICS)169 (71)

	Age (mean): (HD) 67.3, (MD) 66.7, (LD) 64.8, (no ICS) 67.0
	Socioeconomic characteristics: NR
	Other
Evaluated ICS	(high dose (HD)(9500 Kg/d), medium dose (MD)(250È500 Kg/d), and low dose (LD)(G250 Kg/d)
Number of cohorts	N=4 (high dose (HD)(9500 Kg/d), medium dose (MD)(250È500 Kg/d), low dose (LD)(G250 Kg/d), and no ICS
Intervention (ICS)	ICS (Not defined)
Intervention (Control)	No ICS
Adjustment method	NR
Included Outcome/s	Tuberculosis

Study ID	**Suissa 2018**
Study acronym	NA
Reference	Suissa, S., Dell'Aniello, S., & Ernst, P. (2018). Comparative effectiveness of LABA-ICS versus LAMA as initial treatment in COPD targeted by blood eosinophils: a population-based cohort study. The Lancet Respiratory Medicine, 6(11), 855-862.
Sponsor	Canadian Institutes of Health Research, Canadian Foundation for Innovation
Country	UK
Objective	to assess the comparative effectiveness of long acting bronchodilator treatment <u>initiation</u> of COPD, comparing LABA-ICS with LAMAs on the incidence of COPD exacerbations and the risk of pneumonia using a large population-based cohort from real-world, clinical practice data."
Setting	Population-based study – primary care patients.
Design	**Retrospective cohort study**

Study period	Patients with COPD **<u>initiating</u>** treatment with a LAMA or a LABA-ICS from Jan 1, 2002, to Dec 31, 2015.
Follow-up duration	Patients were followed up for **1 year** for the occurrence of a moderate or severe COPD exacerbation and for severe pneumonia.
Data source	UK's Clinical Practice Research Datalink (CPRD) *(contains primary care medical records for over 10 million people enrolled from over 600 practices)* For over half of the practices, the CPRD can be linked to the Hospital Episodes Statistics (HES) database that provides data on hospital admissions.
POPULATION (eligibility)	all patients with a COPD diagnosis who were new users of long-acting bronchodilators, either LABA-ICS or LAMAs, from Jan 1, 2002, until Dec 31, 2015, within the HES-linked population. We excluded patients who initiated treatment with both bronchodilators on the same date. All patients required at least 1 year of medical history and a measure of blood eosinophil concentration before cohort entry, defined by the date of the first cohort-defining prescription to identify new use. To increase the likelihood of a diagnosis of COPD, we included only patients aged 55 years or older at cohort entry.
POPULATION (baseline participant characteristics)	N= 24732 **Time since diagnosis:** NR **Severity of condition:** NR **Presence of other condition:** Smoker 10 592 (85·7%) 11 477 (92·8%) 0·232 Obesity status Obese 3201 (25·9%) 3016 (24·4%) 0·034 Non-obese 7613 (61·6%) 7923 (64·1%) 0·052 Missing data 1552 (12·6%) 1427 (11·5%) 0·031 Alcohol abuse 184 (1·5%) 203 (1·6%) 0·012 **Sex:** Women 5796 (46·9%) 5433 (43·9%) 0·059 Men 6750 (53·1%) 6933 (56·1%) 0·059 **Age:** mean (SD) 71·9 (9·3) 72·0 (8·9) **Socioeconomic characteristics:** NR

	Other:
	inhaled glucocorticoids 4528 (36·6%) 3280 (26·5) 0·218
Evaluated ICS	Fluticasone, budesonide and beclometasona
Number of cohorts	N=2 (LABA-ICS cohort (n=12366) and LAMA cohort (n=12366))
Intervention (ICS)	LABA-ICS (n=12 366) ● fluticasone propionate (65·8%) ● budesonide (27·8%) ● beclomethasone (5·7%) ● Two ICS (0·7%)
Intervention (Control)	LAMA (n=12 366)
Adjustment method	High-dimensional Propensity score (HSPS) The HDPS method selects covariates based on their prevalence and their potential for confounding. We selected the covariates from six data dimensions (medications, procedures and lab data, clinical diagnoses, medical history, administrative information, and hospital diagnoses) measured in the 1-year baseline period before cohort entry. We then used logistic regression to estimate the propensity of initiating LABA-ICS treatment versus LAMA, including the 500 confounders most likely to occur, with respect to exacerbation risk among these. Age, sex and previous exacerbation were forced into the propensity score.
Included Outcome/s	**Primary outcome:** Pneumonia **Secondary outcome:** the occurrence of the first hospital admission for community-acquired pneumonia (serious pneumonia).

Study ID	**Suissa 2019b**
Study acronym	NA
Reference	Suissa, S., Dell'Aniello, S., & Ernst, P. (2019). Comparative effectiveness and safety of LABA-LAMA vs LABA-ICS treatment of COPD in real-world clinical practice. Chest, 155(6), 1158-1165.
Sponsor	Canadian Institutes of Health Research (CIHR) Canada Foundation for Innovation (CFI)

	Boehringer-Ingelheim
Country	UK
Objective	Assess the effectiveness of a combination of LABA-LAMA compared with LABA-ICS on the incidence of COPD exacerbation and the risk of severe pneumonia requiring hospitalization
Setting	Atención Primaria (pacientes en la comunidad)
Design	**Retrospective cohort study** Incident new-user cohort design
Study period	2015 - 2020
Follow-up duration	For up to 1 year from the date of combined treatment initiation, or until the earliest of treatment discontinuation
Data source	**Clinical Practice Research Datalink (CPRD)** A primary care database from the United Kingdom that contains primary care medical records for over 10 million people enrolled from over 600 practices. Trained participating general practitioners record medical information, including demographic data, lifestyle factors, and medical diagnoses, using the Read classification. Prescriptions are automatically transcribed, using the UK Prescription Pricing Authority Dictionary. For over half of the practices, the CPRD can be linked to the Hospital Episode Statistics (HES) database that provides hospitalization data. The recorded information on medications and diagnoses has been validated and shown to be of high quality.
POPULATION (eligibility)	Diagnosis of COPD and who received at least one prescription for a long-acting bronchodilator, either a LABA or LAMA, or for an ICS from January 1, 2002 until December 31, 2015. > 55 years
POPULATION (baseline participant characteristics)	N= 3954 **Time since diagnosis:** NR **Severity of condition:** FEV1 (% predicted),b mean (SD) 53.9 (18.9) 52.7 (19.4) **Presence of other condition:** Smoker, No. (%) 1,867 (94.4) 1,837 (92.9) Obesity status, No. (%) Obese 469 (23.7) 451 (22.8)

	Sex: Female sex, No. (%) 778 (39.4) 778 (39.4)
	Age: Age at cohort entry, y, mean (SD) 71.9 (8.5) 71.8 (8.6)
	Socioeconomic characteristics: NR
	Other
Number of cohorts	N=2 (LABA-LAMA (n=1977) and LABA-ICS (n=1977))
Intervention (ICS)	LABA-ICS (NR dose)
Intervention (Control)	LABA -LAMA (tiotropium) (NR dose)
Adjustment method	Propensity Score. It was computed high-dimensional time-conditional propensity scores by identifying all available data (eg, diagnoses, signs, symptoms, procedures, medications, up to 200 variables) in the 1 year period prior to the date of cohort entry for each time based exposure set.
Included Outcome/s	Pneumonia

Study ID	**TASHKIN 2018**
Study acronym	**UPLIFT**
Reference	Morjaria, J. B., Rigby, A., & Morice, A. H. (2017). Inhaled corticosteroid use and the risk of pneumonia and COPD exacerbations in the UPLIFT study. Lung, 195(3), 281-288.
	Tashkin, D. P., Miravitlles, M., Celli, B. R., Metzdorf, N., Mueller, A., Halpin, D. M., & Anzueto, A. (2018). Concomitant inhaled corticosteroid use and the risk of pneumonia in COPD: a matched-subgroup post hoc analysis of the UPLIFT® trial. Respiratory research, 19(1), 196.
	Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med. 2008;359:1543–54
	Decramer, Marc, et al. "Clinical trial design considerations in assessing long-term functional impacts of tiotropium in COPD: the UPLIFT trial." COPD: Journal of Chronic Obstructive Pulmonary Disease 1.2 (2004): 303-312.
Sponsor	Boerhinger Ingelheim
Country	Multinational (37 countries)

Objective	To determine rate and number of episodes of pneumonia and exacerbations of COPD in patients entering the study on no ICS, fluticasone proprionate (FP), and other ICS.
Setting	490 investigational centers
Design	**Retrospective observational study** This post hoc analysis included ICS-treated patients matched with patients who had not received ICS during the UPLIFT® trial
Study period	2003 - 2008
Follow-up duration	1500 days (4 years)
Data source	UPLIFT trial dataset
POPULATION (eligibility)	All subjects were ≥40 years of age, had a diagnosis of COPD, smoked for ≥10 pack years, were not on long-term oxygen therapy and had not had an exacerbation of COPD or respiratory infection within the last 4 weeks of screening.
POPULATION (baseline participant characteristics)	N= 5992 **Time since diagnosis:** NR **Severity of condition:** FEV1% Pred 39; Severity I/II n=1309 (21.84%) **Presence of other condition:** Current smoker n=1772 (29,57%) **Sex:** (men) n=4473 (74,64%) **Age (mean):** 65 **Socioeconomic characteristics:** Race White 895 (91%) 912 (92%) 804 (92%) 769 (91%) 998 (87%) 1010 (88%) Black 19 (2%) 13 (1%) 4 (<1%) 50 (10%) 96 (8%) 99 (10%) Asian 48 (5%) 43 (4%) 41 (5%) 21 (3%) 22 (2%) 18 (2%) **Other**
Evaluated ICS	Fluticasone and ICS (type not specified)

Number of cohorts	N=2 (ICS (n=3700) vs no ICS (n=2292)); then stratified to six groups (Fluticasone Placebo (n=987), Fluticasone Tiotropium (n=994), Other ICS Placebo (n=873), Other ICS Tiotropium (n=846), No ICS Placebo (n=1146) and No ICS Tiotropium (n=1146))
Intervention (ICS)	Fluticasone Placebo, Fluticasone Tiotropium, Other ICS Placebo and Other ICS Tiotropium
Intervention (Control)	No ICS Placebo and No ICS Tiotropium
Adjustment method	Poisson regression was used to compare the frequency of respiratory adverse events. At entry, the groups were well matched apart from a higher FEV1% predicted (38 vs. 41%; ICS vs. no ICS, respectively) and prevalence of current smoking (26 vs. 36%; ICS vs. no ICS, respectively).
Included Outcome/s	Pneumonia

Study ID	**Wang 2019**
Study acronym	NA
Reference	Wang, C. Y., Lin, Y. S., Wang, Y. H., Lai, C. C., Wang, H. C., Chen, L., & Yu, C. J. (2019). Risk of sepsis among patients with COPD treated with fixed combinations of inhaled corticosteroids and long-acting Beta2 agonists. Aging (Albany NY), 11(17), 6863.
Sponsor	Taiwan National Science Foundation
Country	Taiwan
Objective	To assess the effect of Budesonide/Formoterol and Fluticasone/Salmeterol on Sepsis risk
Setting	Population-based
Design	**RETROSPECTIVE COHORT STUDY**
Study period	2004 - 2011
Follow-up duration	7 years
Data source	Taiwan National Health Insurance Research Database
POPULATION (eligibility)	International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 491, 492, and 496 were used to identify patients with COPD. Only patients with at least three outpatient or inpatient visits for COPD and those aged between 40 and 100 years were included.
POPULATION (baseline participant characteristics)	Initially, a total of 17,111 patients had the diagnosis of COPD and received a fixed ICS/LABA combination (10,267 patients with fluticasone/salmeterol and 6,844 patients with

	budesonide/formoterol) were identified after excluding those with previous sepsis. Then, pairwise matching (1:1) resulted in two similar subgroups, with 6,688 patients in each.
Evaluated ICS	fluticasone budesonide
Number of cohorts	N=2 (Fluticasone/salmeterol (n=6688) and Budesonide/formoterol (n=6688))
Intervention (ICS)	NR
Intervention (Control)	NA
Adjustment method	NA
Included Outcome/s	LRTI, TB and Sepsis The primary outcome was sepsis, which was defined using ICD-9-CM codes as previously reported.[16] Only the first episode of sepsis was included

Study ID	**Wu 2016**
Study acronym	**NA**
Reference	Wu MF, Jian ZH, Huang JY, Jan CF, Nfor ON, Jhang KM, Ku WY, Ho CC, Lung CC, Pan HH, Wu MC, Liaw YP. Post-inhaled corticosteroid pulmonary tuberculosis and pneumonia increases lung cancer in patients with COPD. BMC Cancer. 2016 Oct 10;16(1):778. doi: 10.1186/s12885-016-2838-4. PMID: 27724847; PMCID: PMC5057453.
Sponsor	NA
Country	Taiwan
Objective	To evaluate the association between post-ICS pulmonary infections and lung cancer using the National Health Insurance Research Database (NHIRD).
Setting	Using inpatient and outpatient medical records.
Design	**Retrospective cohort study**
Study period	2001 to 2005
Follow-up duration	Followed up until the development of lung cancer, loss to follow-up, death, or the end of the year 2010.
Data source	Taiwan National Health Insurance Research database (NHIRD)

POPULATION (eligibility)	Eligible participants included COPD patients who were first time users of ICS prescribed for a period of 3 months or more. This study enrolled patients with COPD from 2001 to 2005 who were free from lung cancer before 2002.
POPULATION (baseline participant characteristics)	N= ICS (n=8813), no ICS (n=35,252) **Time since diagnosis:** NR **Severity of condition:** NR **Presence of other condition:** **Sex:** (men %) ICS 69.0, no ICS 69.0 **Age:** [60-79] ICS 60.4%, no ICS 60.4% **Socioeconomic characteristics:** **Other**
Number of cohorts	N=2 (ICS users and no ICS users)
Intervention (ICS)	ICS (not specified)
Intervention (Control)	No ICS
Adjustment method	Cox proportional hazards regression modelling.
Included Outcome/s	Pneumonia, tuberculosis

Study ID	Yang 2017
Study acronym	TCORE
Reference	Yang, H. H., Lai, C. C., Wang, Y. H., Yang, W. C., Wang, C. Y., Wang, H. C., ... & Yu, C. J. (2017). Severe exacerbation and pneumonia in COPD patients treated with fixed combinations of inhaled corticosteroid and long-acting beta2 agonist. International journal of chronic obstructive pulmonary disease, 12, 2477.
Sponsor	National Science Council and from National Health Research Institutes (intramural funding)
Country	Taiwan

Objective	We conducted a comparative study of those who used budesonide/formoterol and those treated with fluticasone/salmeterol for COPD.
Setting	Population-based study
Design	**Retrospective cohort study** Population-based cohort study
Study period	1997-2010
Follow-up duration	This cohort was followed longitudinally from 1997 to 2010.
Data source	Taiwan National Health Insurance Research database (NHIRD) NHIRD consists of standard computerized claims documents submitted by medical institutions seeking reimbursement through the National Health Insurance (NHI) program. The NHI program provides the medical needs for more than 23 million people, representing 98% of the population in Taiwan, and records clinical diagnoses according to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.
POPULATION (eligibility)	Patients with COPD who were treated with a fixed combination of budesonide/formoterol or fluticasone/salmeterol. Adult patients with COPD ≥40 and ≤100 years were identified using ICD-9-CM codes 491, 492, and 496. Inclusion criteria included a record of at least three outpatient or one inpatient visits for COPD and ever undergone a lung function test within 1 year before and after the diagnosis of COPD had been established. Thus, a total of 141,855 patients were identified as having COPD. Of those patients, only 18,956 patients received a fixed ICS and LABA combination (budesonide/formoterol Turbuhaler or fluticasone/salmeterol Accuhaler or Metered Dose Inhaler). The index date was defined as the date of the first fixed ICS/LABA combination prescription after COPD had been diagnosed.

POPULATION (baseline participant characteristics)	N= 14590
	
	Time since diagnosis: NR
	
	Severity of condition:
	
	COPD severe AE:
	
	  0: 60.90% - 61.10%
	
	  1: 15.38% - 14.94%
	
	  ≥2: 23.71% - 23.96%

	Sex: (Male) 73.83% - 73.47%
	Age (mean year): 63.66±10.33 - 63.53±10.30
	Socioeconomic characteristics:
	Monthly income, n (%)
	<19100 33.65%
	19100-41999 52.16%
	>=42000 14.19%
	Other
Number of cohorts	N=2 (Fluticasone/salmeterol (N=7295) and Budesonide/formoterol (N=7295))
Intervention (ICS)	Both groups include ICS:
	-Patients receiving fluticasone/salmeterol
	-Patients receiving budesonide/formoterol
Intervention (Control)	NA
Adjustment method	Propensity score
	Patients treated with either treatment combination were matched on the following criteria: age, sex, number of prescriptions for antibiotics, oral steroids, ICS, long-acting and short-acting bronchodilators, diagnosis of diabetes, cancer, heart failure, hypertension, stroke, and the number of previous severe COPD exacerbations – COPD-related hospitalizations or emergency department visits
Included Outcome/s	Pneumonia*
	*Pneumonia was defined as COPD patients who developed pneumonia requiring emergency department or hospital admission. Pneumonia requiring mechanical ventilation. Pneumonia requiring mechanical ventilation (MV) was defined as COPD patients with pneumonia and using MV for respiratory failure

Study ID	**Yawn 2013**
Study acronym	NA
Reference	Yawn, B. P., Li, Y., Tian, H., Zhang, J., Arcona, S., & Kahler, K. H. (2013). Inhaled corticosteroid use in patients with chronic

	obstructive pulmonary disease and the risk of pneumonia: a retrospective claims data analysis. International journal of chronic obstructive pulmonary disease, 8, 295.
Sponsor	Novartis
Country	USA
Objective	Using claims databases as a research model of real-world diagnosis and treatment, to determine if the use and dose of inhaled corticosteroids (ICS) among patients with newly diagnosed COPD are associated with increased risk of pneumonia.
Setting	Population-based
Design	**Retrospective cohort study** Retrospective cohort analysis
Study period	2006-2010
Follow-up duration	Follow up period (days): mean 669 (502) and median 573 (range 2–1826)
Data source	Two MarketScan® databases (Arlington, VA, USA) were used: Commercial Claims and Encounters (CCE) and CMS Supplemental and Coordination of Benefits (COB), covering the years 2005–2010. These databases capture person-specific clinical utilization, expenditures, and enrolment across inpatient, outpatient, prescription drug, and carve-out services (specialist care contracted out from within the plan) from approximately 40 million patients per year from a selection of large employers, health plans, and government and public organizations.
POPULATION (eligibility)	Only newly diagnosed patients (≥45 years) with COPD[1], defined as no COPD diagnosis in the previous 12 months prior to the index date, were included in the study. Patients using oral corticosteroids during the baseline or follow up were excluded. [1]COPD = ICD-9 codes for chronic bronchitis [491.x], emphysema [492.x], or chronic airway obstruction [496]. Pneumonia events included all diagnoses (ICD-9 codes 480.x to 486.x, and 487.0), derived from outpatient, emergency department, or inpatient records.
POPULATION (baseline participant characteristics)	NOTE: the paper does not provide a description (baseline demographic and clinical characteristics) of ICS users vs no ICS users, but patients with pneumonia vs patients with no pneumonia.

	Presence of other condition: Diabetes 20.4% HTA 41.9% **Age:** (mean, SD) 66.99 (12.66) (media, IQR) 65 (45–111) **Sex:** (Male %) 51.9%
Number of cohorts	N=2 (ICS use (N=5677 p/y) and No ICS use (N=237,420 p/y))
Evaluated ICS	ICS exposure was defined as a prescription drug claim for inhaled beclometasone, budesonide (monotherapy and fixed dose combination with formoterol), triamcinolone, fluticasone (monotherapy and fixed dose combination with salmeterol), mometasone, and flunisolide.
Intervention (Control)	No ICS use
Adjustment method	A Cox proportional hazard model was used to assess the association of ICS use and risk of pneumonia, controlling for baseline characteristics.
Included Outcome/s	Pneumonia

NESTED CASE CONTROL STUDIES

Study ID	**Andréjak 2013**
Study acronym	**NA**
Reference	Andréjak, C., Nielsen, R., Thomsen, V. Ø., Duhaut, P., Sørensen, H. T., & Thomsen, R. W. (2013). Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis. Thorax, 68(3), 256-262.
Sponsor	Denmark
Country	This study examined chronic respiratory diseases and ICS use as risk factors in a population-based case-control study encompassing all adults in Denmark with microbiologically confirmed NTM pulmonary disease between 1997 and 2008.
Design	**Case–control study design**

Data source	Danish National Registry of Patients, the prescription database and the Danish Central Population Registry.
POPULATION (baseline participant characteristics)	N=2 (Cases non-tuberculous mycobacteriosis (n=332) and controls (10 matched population controls per case, n=3320))
Evaluated ICS	Beclometasone, mometasone, fluticasone and budesonide
Included Outcome/s	Non-tuberculous mycobacterial infection

Study ID	Brassard 2010
Study acronym	NA
Reference	Brassard, P., Suissa, S., Kezouh, A., & Ernst, P. (2011). Inhaled corticosteroids and risk of tuberculosis in patients with respiratory diseases. American journal of respiratory and critical care medicine, 183(5), 675-678.
Sponsor	Canada
Country	To quantify the independent contribution of ICS to the risk of TB among a population of patients with airway diseases.
Design	A population-based cohort design with a nested case-control analysis was used.
Data source	Quebec databases.
POPULATION (baseline participant characteristics)	N= Cases 564 Control 5640

TB cases were identified, and age-matched control subjects were selected from all subjects who entered the cohort in the same month as the cases. TB incidence among the cohort was compared with the general population of Quebec using the standardized incidence ratio. |
| Evaluated ICS | All forms of prescribed ICS were examined during the 12-month period preceding the index date. ICS included oral inhaled beclomethasone, budesonide, triamcinolone, fluticasone, and flunisolide, whether dispensed alone or in a combination inhaler with an inhaled b-agonist. |
| Included Outcome/s | TBC |

Study ID	Brode 2017
Study acronym	NA
Reference	Brode, S. K., Campitelli, M. A., Kwong, J. C., Lu, H., Marchand-Austin, A., Gershon, A. S., ... & Marras, T. K. (2017). The risk of mycobacterial infections associated with inhaled corticosteroid use. European Respiratory Journal, 50(3), 1700037.
Sponsor	Canada
Country	to determine if ICS use is associated with an increased risk of nontuberculous mycobacterial pulmonary disease (NTM-PD) or tuberculosis (TB)
Design	Population-based nested case–control study
Data source	Health administrative data at the Institute for Clinical Evaluative Sciences (Toronto, ON, Canada) were used to identify cohort patients with OLD, demographics [19], vital status, comorbidities [20–24] and drug exposure (see supplementary material for details). Asthma and COPD were identified using validated algorithms [25, 26], and ACOS was defined when a patient met criteria for both asthma and COPD (not previously validated). Mycobacterial infections were identified with Public Health Ontario's (Toronto, ON, Canada) laboratory information system, which captures ~95% of NTM isolates and 100% of TB isolates in the province [27]. See supplementary material for mycobacterial culture methods.
POPULATION (baseline participant characteristics)	N= NTM-PD cases n=2966 NTM-PD controls n=11851 TB cases n=327 TB controls n=1308
Evaluated ICS	Beclomethasone, budesonide, ciclesonide, fluticasone propionate or momethason
Included Outcome/s	Tuberculosis and other

Study ID	Cascini 2017
Study acronym	OUTPUL
Reference	Cascini, S., Kirchmayer, U., Belleudi, V., Bauleo, L., Pistelli, R., Di Martino, M., ... & Agabiti, N. (2017). Inhaled corticosteroid use in chronic obstructive pulmonary disease and risk of pneumonia: a nested case-control population-based study in Lazio (Italy)—The OUTPUL Study. COPD: Journal of Chronic Obstructive Pulmonary Disease, 14(3), 311-317.
Sponsor	Italy
Country	to determine if ICS use if ICS use, with or without long-active b2 agonist, increase pneumonia risk in COPD patients
Design	Nested case-control study in a prospective cohort of patients
Data source	Electronic healthcare records ("The OUTPUL study")
POPULATION (baseline participant characteristics)	Pneumonia cases (N=3141) Controls (N=12564) 45% were men and aged 75.5 (±9.9) years.
Evaluated ICS	ICS comprised beclometasone, budesonide, flunisolide, betamethasone, fluticasone, triamcinolone, mometasone, ciclesonide, fluticasone furoate, salbutamol and sodium cromoglicate
Included Outcome/s	Pneumonia

Study ID	Ernst 2007
Study acronym	NA
Reference	Ernst, P., Gonzalez, A. V., Brassard, P., & Suissa, S. (2007). Inhaled corticosteroid use in chronic obstructive pulmonary disease and the risk of hospitalization for pneumonia. American journal of respiratory and critical care medicine, 176(2), 162-166
Sponsor	Canada

Country	To examine whether these medications might be associated with an excess risk of pneumonia
Design	**Nested case-control study within a cohort of patient**
Data source	Health databases of the Re´gie de l'Assurance Maladie du Que´bec (RAMQ, Quebec City, PQ, Canada), the agency responsible for administering the universal health insurance program of the province of Quebec, Canada
POPULATION (baseline participant characteristics)	Case Subjects (N=23,942) Control Subjects Number (N=95,768)
Evaluated ICS	ICS included orally inhaled beclomethasone, budesonide, triamcinolone, fluticasone, and flunisolide, whether dispensed alone or in a combination inhaler with an inhaled-agonist.
Included Outcome/s	Pneumonia

Study ID	**Ernst 2016**
Study acronym	**NA**
Reference	Ernst, P., Coulombe, J., Brassard, P., & Suissa, S. (2017). The risk of sepsis with inhaled and oral corticosteroids in patients with COPD. COPD: Journal of Chronic Obstructive Pulmonary Disease, 14(2), 137-142.
Sponsor	Canada
Country	examine the risk of sepsis in subjects with respiratory disease treated with inhaled and oral corticosteroids between 1990 and 2007.
Design	**QUASI-COHORT STUDY** A quasi-cohort analysis, based on the nested case-control approach within the cohort,
Data source	databases of the Régie de l'assurance maladie du Québec (RAMQ), the health insurance program of the province of Québec, Canada.

POPULATION (baseline participant characteristics)	The cohort included N=163,514 patients treated for COPD, including 1,704 who were hospitalized for or died with sepsis during follow-up (incidence rate 1.94 per 1000 per year).
Evaluated ICS	Beclomethasone, fluticasone, budesonide, triamcinolone and flunisolide.
Included Outcome/s	Sepsis

Study ID	Gayle 2019
Study acronym	NA
Reference	Gayle, A., Dickinson, S., Poole, C., Pang, M., Fauconnot, O., & Quint, J. K. (2019). Incidence of type II diabetes in chronic obstructive pulmonary disease: a nested case–control study. NPJ primary care respiratory medicine, 29(1), 1-6.
Sponsor	UK
Country	To investigate the incidence of type II diabetes mellitus (T2DM) among people with COPD and whether exposure to inhaled corticosteroid (ICS) and exacerbation status was associated with T2DM
Design	Nested case–control study
Data source	Clinical Practice Research Datalink (CPRD)
POPULATION (baseline participant characteristics)	N= We identified 220,971 COPD patients; mean age at COPD diagnosis was 66 years (SD 12) and 54% were male.
Evaluated ICS	Budesonide
Included Outcome/s	Diabetes

Study ID	Gonzalez 2010
Study acronym	NA

Reference	Gonzalez, A. V., Li, G., Suissa, S., & Ernst, P. (2010). Risk of glaucoma in elderly patients treated with inhaled corticosteroids for chronic airflow obstruction. Pulmonary pharmacology & therapeutics, 23(2), 65-70.
Country	Canada
Objective	To determine the risk of new onset ocular hypertension or glaucoma requiring treatment, associated with the use of ICS in elderly patients treated for airways disease.
Design	**Nested case–control study**
Data source	Databases from the Quebec provincial health insurance plan.
POPULATION (baseline participant characteristics)	N= 2291 cases and 13445 age-matched controls A cohort of patients receiving respiratory medications was formed among all subjects 66 years of age and older. Cases were subjects in whom treatment for glaucoma was initiated between January 1, 1988 and December 31, 2003 after a first ever visit to an ophthalmologist within the preceding 90 days. Age-matched controls were selected among individuals who also visited an ophthalmologist for the first time within 90 days of the case's treatment date and did not receive a treatment for glaucoma.
Evaluated ICS	beclomethasone, budesonide, triamcinolone, fluticasone, and flunisolide.
Included Outcome/s	Eye disorder

Study ID	**Gonzalez 2018**
Study acronym	**NA**
Reference	Gonzalez, A. V., Coulombe, J., Ernst, P., & Suissa, S. (2018). Long-term use of inhaled corticosteroids in COPD and the risk of fracture. Chest, 153(2), 321-328.
Country	Canada
Objective	To assess whether long-term ICS use in patients with COPD increases the risk of hip or upper extremity fractures, and examined sex-related differences.

Design	Nested case-control study
Data source	The Quebec healthcare databases
POPULATION (baseline participant characteristics)	N= Fracture cases (n=19,396) Controls (n=384,478) The study used a population-based cohort of patients with COPD, aged 55 or older, that was followed for the occurrence of a hip or upper extremity fracture. In view of the large size of the cohort, the high number of fractures and the time-varying nature of ICS prescriptions, a nested case-control analysis within the cohort was performed.
Evaluated ICS	ICS (not determined)
Included Outcome/s	Fracture

Study ID	Jick 2001
Study acronym	NA
Reference	Jick, S. S., Vasilakis-Scaramozza, C., & Maier, W. C. (2001). The risk of cataract among users of inhaled steroids. Epidemiology, 229-234.
Country	UK
Objective	To compare the incidence rate of cataracts among users of inhaled formulations of beclomethasone, budesonide, and fluticasone with the rate among those without a history of steroid use.
Design	Nested case control study
Data source	United Kingdom–based General Practice Database
POPULATION (baseline participant characteristics)	N= We identified 1,194 cases of cataract and 2,387 matched controls (ie those who did not have a cataract diagnosis) from the base cohort of non-users and inhaled steroid users. The mean age was 73.1 years in both cases and controls (range 3–90). Fifty eight percent of subjects were female, 9% had received only one

	prescription for an inhaled steroid, while 14% had received more than 20 prescriptions.
Evaluated ICS	beclomethasone, budesonide, and fluticasone
Included Outcome/s	Eye disorder

Study ID	**Johannes 2005**
Study acronym	**NA**
Reference	Johannes, C. B., Schneider, G. A., Dube, T. J., Alfredson, T. D., Davis, K. J., & Walker, A. M. (2005). The risk of nonvertebral fracture related to inhaled corticosteroid exposure among adults with chronic respiratory disease. Chest, 127(1), 89-97.
Country	United States
Objective	To examine nonvertebral fracture risk in relation to inhaled corticosteroid (ICS) exposure among adults with respiratory disease.
Design	**Nested case control study**
Data source	Ingenix Epidemiology (Auburndale, MA) maintains a research database of UnitedHealthcare members who have both medical and prescription benefit coverage
POPULATION (baseline participant characteristics)	N= Cases (n=1,722) represented patients with a first treated nonvertebral fracture (the index date is the first fracture claim). Control subjects (n=17,220) were randomly selected from the person-time and assigned a random index date.
Evaluated ICS	Fluticasone, beclomethasone dipropionate, budesonide, flunisolide, and triamcinolone
Included Outcome/s	Fracture

Study ID	**Joo 2010**

Study acronym	NA
Reference	Joo, M. J., Au, D. H., Fitzgibbon, M. L., & Lee, T. A. (2010). Inhaled corticosteroids and risk of pneumonia in newly diagnosed COPD. Respiratory medicine, 104(2), 246-252.
Country	United State
Objective	To determine if the use of ICS among newly diagnosed COPD patients is associated with an increased risk of pneumonia hospitalizations.
Design	**Nested case-control study**
Data source	data from the Department of Veterans Affairs and Centers for Medicare and Medicaid Services
POPULATION (baseline participant characteristics)	N= total of 145,586 were included in the cohort. From this cohort, a total of 13,995 cases were matched to 131,591 controls (average of 9.4 controls/case). The population was predominantly male (cases = 99.1%, controls = 99.8%) and the average age was 75.4 (SD = 5.6) years for the cases and 75.0(SD= 5.4) years for the controls
Evaluated ICS	ICS included orally inhaled beclomethasone, budesonide, flunisolide, fluticasone, and triamcinolone. Doses were converted to beclomethasone equivalents18 and cumulative exposure was calculated.
Included Outcome/s	Pneumonia

Study ID	**Lee 2004**
Study acronym	**NA**
Reference	Lee, T. A., & Weiss, K. B. (2004). Fracture risk associated with inhaled corticosteroid use in chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine, 169(7), 855-859.
Country	United States

Objective	To examine the association between nonvertebral fractures in patients with COPD and the use of ICS in the Veterans Affairs population.
Design	**Nested case control study**
Data source	A nested case–control study in a cohort of Veterans Affairs patients with COPD. Veterans Affairs inpatient, outpatient, pharmacy, and beneficiary databases were used
POPULATION (baseline participant characteristics)	N= 1,708 cases were matched to 6,817 control patients 94%male, average age was 62.7 years (SD 12.4) in both cases and control patients (Table 1). The average follow-up time was nearly 1.75 years (637 days in cases and 635 days in control patients).
Evaluated ICS	NR
Included Outcome/s	Fracture

Study ID	**Lee 2013**
Study acronym	**NA**
Reference	Lee, C. H., Kim, K., Hyun, M. K., Jang, E. J., Lee, N. R., & Yim, J. J. (2013). Use of inhaled corticosteroids and the risk of tuberculosis. Thorax, 68(12), 1105-1113.
Country	South Korea
Objective	To elucidate the association between ICS use and development of TB among patients with various respiratory diseases in South Korea, an intermediate-TB- burden country.
Design	**Nested case-control study**
Data source	Korean national claims database
POPULATION (baseline participant characteristics)	N= Patients diagnosed as having TB after initiation of inhaled medication were included as cases. For each case individual, up to five control individuals matched for age, sex, diagnosis of asthma

	or chronic obstructive pulmonary disease (COPD) and initiation date of inhaler use were selected. They matched 4139 individuals diagnosed as having TB with 20 583 controls.
Evaluated ICS	Beclomethasone, budesonide, triamcinolone, ciclesonide, fluticasone, or flunisolide
Included Outcome/s	Tuberculosis

Study ID	**Lu 2017**
Study acronym	**NA**
Reference	Lu, P. C., Yang, Y. H., Guo, S. E., & Yang, T. M. (2017). Factors associated with osteoporosis in patients with chronic obstructive pulmonary disease—a nationwide retrospective study. Osteoporosis International, 28(1), 359-367.
Country	China
Objective	to identify the factors associated with osteoporosis in patients with chronic obstructive pulmonary disease in Taiwan.
Design	**Nested case-control study**
Data source	National Health Insurance Research Database from 1997 to 2009.
POPULATION (baseline participant characteristics)	N= COPD patients with osteoporosis (n =4,078) COPD patients without osteoporosis (n =41,317)
Evaluated ICS	NR
Included Outcome/s	BMD (Osteoporosis)

Study ID	**Mapel 2010**
Study acronym	**NA**

Reference	Mapel D, Schum M, Yood M, Brown J, Miller D, Davis K. Pneumonia among COPD patients using inhaled corticosteroids and long-acting bronchodilators. Prim Care Respir J. 2010 Jun;19(2):109-17. doi: 10.4104/pcrj.2009.00072. PMID: 20082059; PMCID: PMC6602217.
Country	US
Objective	To assess the risk of pneumonia among COPD patients using salmeterol/fluticasone propionate combination inhalers (SFC), inhaled corticosteroids (ICS), or long-acting beta-agonists (LABA), alone or in combination, compared to those using only short-acting bronchodilators (SABD).
Design	**Nested case-control study**
Data source	Databases of three large regional managed care organisations from different parts of the USA between 1st September 2001 and 31st August 2003.
POPULATION (baseline participant characteristics)	N= patients with pneumonia (n= 2154)
Evaluated ICS	Salmeterol/fluticasone propionate combination inhalers (SFC), or inhaled corticosteroids (ICS)
Included Outcome/s	Pneumonia* * Pneumonia cases were defined as patients with any pneumonia-related ICD diagnosis code (ICD-9 codes 480.0 through 487.0) in an outpatient, emergency room, or inpatient setting.

Study ID	**Miller 2010**
Study acronym	**NA**
Reference	Miller, D. P., Watkins, S. E., Sampson, T., & Davis, K. J. (2010). Long-term use of fluticasone propionate/salmeterol fixed-dose combination and incidence of nonvertebral fractures among patients with COPD in the UK General Practice Research Database. The Physician and sportsmedicine, 38(4), 19-27.
Country	UK
Objective	to examine the association between ICS exposure (alone and in a fixed combination with salmeterol) and risk of nonvertebral fractures in a case-control study nested within a cohort of patients with COPD in the UK General Practice Research Database (GPRD).
Design	**Nested case-control study**

Data source	UK General Practice Research Database
POPULATION (baseline participant characteristics)	N= Fracture Cases: (n = 1523) Controls: (n = 3749)
Evaluated ICS	fluticasona
Included Outcome/s	Fracture

Study ID	**Miller 2011**
Study acronym	**NA**
Reference	Miller, D. P., Watkins, S. E., Sampson, T., & Davis, K. J. (2011). Long-term use of fluticasone propionate/salmeterol fixed-dose combination and incidence of cataracts and glaucoma among chronic obstructive pulmonary disease patients in the UK General Practice Research Database. International journal of chronic obstructive pulmonary disease, 6, 467.
Country	UK
Objective	To evaluate the association between use of ICS-containing products, specifically fluticasone propionate/salmeterol fixed-dose combination (FSC), and incidence of cataracts and glaucoma among patients with COPD in a large electronic medical record database in the United Kingdom.
Design	**Nested case-control study**
Data source	UK General Practice Research Database
POPULATION (baseline participant characteristics)	N= The cohort included 53,191 patients with COPD. We matched 2404 of the 2941 cataract cases to 5621 controls by age, gender, general practice, and length of time in the cohort. Of the 327 glaucoma cases, 273 were matched by age, gender, general practice, and length of time in the cohort to 703 controls
Evaluated ICS	Fluticasona

Included Outcome/s	Eye disorder

Study ID	**Pujades-Rodriguez 2007**
Study acronym	**NA**
Reference	Pujades-Rodriguez, M., Smith, C. J. P., & Hubbard, R. B. (2007). Inhaled corticosteroids and the risk of fracture in chronic obstructive pulmonary disease. QJM: An International Journal of Medicine, 100(8), 509-517.
Country	UK
Objective	To quantify the dose–response relationship between fracture risk and inhaled corticosteroids in people with COPD, independent of the effects of percent predicted FEV1 and oral corticosteroids.
Design	Nested case control analysis
Data source	The Health Improvement Network database
POPULATION (baseline participant characteristics)	N= Cases and controls were COPD patients aged 540 years or more at diagnosis, with a FEV1 measurement up to 5 July 2005. Cases (people with a fracture event after 1 January 1998, n 1⁄4 1235) were assigned up to four controls (n 1⁄4 4598), matched by gender and general practice.
Evaluated ICS	Beclometasone dipropionate was the most commonly prescribed inhaled corticosteroid with 66% of the prescriptions followed by fluticasone propionate (18%) and then budesonide (16%).
Included Outcome/s	Fracture

Study ID	**Suissa 2010**
Study acronym	**NA**

Reference	Suissa, S., Kezouh, A., & Ernst, P. (2010). Inhaled corticosteroids and the risks of diabetes onset and progression. The American journal of medicine, 123(11), 1001-1006.
Country	Canada
Objective	disease to assess whether the use and the dose of inhaled corticosteroids increase the risk of new diabetes onset and, among patients who also have existing type 2 diabetes, whether inhaled corticosteroid use leads to the need for insulin.
Design	In view of the large sizes of the 2 cohorts, a nested case-control analysis within each cohort was performed. For each case, 10 controls matched on age (within 1 year) and calendar time were selected at random from all subjects who entered the cohort in the same month as the case and at risk (alive and without the outcome of interest) on the date the case event occurred (index date). When fewer than 10 potential controls were available for a case, all members of the risk set were included as controls for that case.
Data source	Régie de l'assurance maladie du Québec
POPULATION (baseline participant characteristics)	N= New Diabetes Onset: Cases (N=30167), Control (N=301096) Diabetes Progression: Cases (N=2099), Controls (N=20763)
Evaluated ICS	Beclomethasone, budesonide, triamcinolone, fluticasone, and flunisolide.
Included Outcome/s	DBT

Study ID	**Suissa 2013**
Study acronym	**NA**
Reference	Suissa, S., Patenaude, V., Lapi, F., & Ernst, P. (2013). Inhaled corticosteroids in COPD and the risk of serious pneumonia. Thorax, 68(11), 1029-1036.
Country	Canada
Objective	To assess whether the different ICS vary in their risk of pneumonia and to evaluate the dose–response effects.

Design	A nested case–control study
Data source	Régie de l'assurance maladie du Québec (RAMQ)
POPULATION (baseline participant characteristics)	N= Pneumonia cases (20,344) and controls (197,705)
Evaluated ICS	Beclomethasone, fluticasone, budesonide, triamcinolone and flunisolide.
Included Outcome/s	Pneumonia

Study ID	Suissa 2015
Study acronym	NA
Reference	Suissa, S., Coulombe, J., & Ernst, P. (2015). Discontinuation of inhaled corticosteroids in COPD and the risk reduction of pneumonia. Chest, 148(5), 1177-1183.
Country	Canada
Objective	To estimate the rate ratio of serious pneumonia associated with discontinuation of ICS use compared with continued use, adjusted for age, sex, respiratory disease severity, and comorbidity.
Design	Nested case-control study
Data source	Quebec health insurance databases,
POPULATION (baseline participant characteristics)	N= Pneumonia Case 14,020 Control 132,697
Evaluated ICS	Fluticasone and budesonide
Included Outcome/s	Pneumonia

Study ID	Thornton 2012
Study acronym	NA
Reference	Thornton Snider, J., Luna, Y., Wong, K. S., Zhang, J., Chen, S. S., Gless, P. J., & Goldman, D. P. (2012). Inhaled corticosteroids and the risk of pneumonia in Medicare patients with COPD. Current medical research and opinion, 28(12), 1959-1967.
Country	US
Objective	To determine the association between inhaled corticosteroid (ICS) use and the risk of pneumonia among Medicare patients with COPD
Design	Nested case-control analysis
Data source	Medicare
POPULATION (baseline participant characteristics)	N= Cases (n = 13,778) Controls (n = 36,767)
Evaluated ICS	Fluticasone, flunisolide, budesonide, beclomethasone, triamcinolone, and mometasone
Included Outcome/s	Pneumonia

Study ID	Wang 2016
Study acronym	IMPACT
Reference	Wang CY, Lai CC, Yang WC, Lin CC, Chen L, Wang HC, Yu CJ. The association between inhaled corticosteroid and pneumonia in COPD patients: the improvement of patients' life quality with COPD in Taiwan (IMPACT) study. Int J Chron Obstruct Pulmon Dis. 2016 Nov 8;11:2775-2783. doi: 10.2147/COPD.S116750. PMID: 27877031; PMCID: PMC5108503.
Country	Taiwan
Objective	To investigate the association between inhaled corticosteroid (ICS) exposure patterns and the risk of pneumonia in chronic obstructive pulmonary disease (COPD) patients.
Design	Nested case-control study

Data source	Database constructed by the National Health Research Institutes of Taiwan
POPULATION (baseline participant characteristics)	N= 51,739 patients, including 19,838 cases of pneumonia, were matched to 74,849 control subjects selected from a cohort of COPD patients using ICSs
Evaluated ICS	Fluticasone/salmeterol, fluticasone
Included Outcome/s	Pneumonia* * All individuals in the study cohort with the serious pneumonia diagnosis codes (ICD-9-CM codes 480–486 and 507) were identified as cases. Serious pneumonia was defined as a hospitalization for or death from pneumonia.