Risk of fractures with inhaled corticosteroids in COPD: systematic review and meta-analysis of randomised controlled trials and observational studies

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ABSTRACT

Background The effect of inhaled corticosteroids (ICS) on fracture risk in patients with chronic obstructive pulmonary disease (COPD) remains uncertain. The aim of this study was to evaluate the association between ICS and fractures in COPD.

Methods MEDLINE, EMBASE, regulatory documents and company registries were searched up to August 2010. Randomised controlled trials (RCTs) of budesonide or fluticasone versus control treatment for COPD (≥24 weeks duration) and controlled observational studies reporting on fracture risk with ICS exposure vs no exposure in COPD were included. Peto OR meta-analysis was used for fracture risk from RCTs while ORs from observational studies were pooled using the fixed effect inverse variance method. Dose–response analysis was conducted using variance-weighted least squares regression in the observational studies. Heterogeneity was assessed using the I^2 statistic.

Results Sixteen RCTs (14 fluticasone, 2 budesonide) with 17 513 participants, and seven observational studies (n=69 000 participants) were included in the meta-analysis. ICSs were associated with a significantly increased risk of fractures (Peto OR 1.27; 95% CI 1.01 to 1.58; p=0.04; I^2=0%) in the RCTs. In the observational studies, ICS exposure was associated with a significantly increased risk of fractures (OR 1.21; 95% CI 1.12 to 1.32; p<0.001; I^2=37%), with each 500 μg increase in beclomethasone dose equivalents associated with a 9% increased risk of fractures, OR 1.09 (95% CI 1.06 to 1.12; p<0.001).

Conclusion Among patients with COPD, long-term exposure to fluticasone and budesonide is consistently associated with a modest but statistically significant increased likelihood of fractures.

Key messages

What is the key question?

- Does long-term use of inhaled corticosteroids increase the risk of fractures in patients with chronic obstructive pulmonary disease (COPD)?

What is the bottom line?

- Our meta-analysis shows that inhaled corticosteroid use is associated with a modest but statistically significant increase in the risk of fractures in patients with COPD.

Why read on?

- The consistency and similarity of the point estimates across randomised trials and observational study designs, and the presence of a dose–response effect in the observational studies lends credibility to this clinically important association.

BACKGROUND

The inhaled corticosteroids (ICS) fluticasone propionate and budesonide are widely used in the treatment of chronic obstructive pulmonary disease (COPD).[1] The Global Initiative for Chronic Obstructive Lung Disease guidelines recommend ICS in combination with long-acting β_2-agonists (LABAs) in moderate to severe COPD to reduce the frequency of exacerbations,[2] and current formulations of ICS approved for use in COPD are fluticasone with salmeterol, and budesonide with formoterol. The potential benefits of ICS are counterbalanced by their systemic adverse effects such as pneumonia and their potential to negatively impact bone health.[3 4]

Prior evidence on the adverse skeletal effects of ICS has been inconsistent. Published evaluations of bone mineral density (BMD) with ICS exposure are limited by considerable losses to follow-up in three large randomised controlled trials (RCTs), with bone density data available only in selected participants.[5–7] Two trials (one fluticasone, one budesonide) reported no significant adverse effect on BMD, perhaps due to inadequate statistical power.[5 6] In the Towards a Revolution in COPD Health (TORCH) subset, patients on salmeterol had a small gain in spine BMD, as compared with patients receiving salmeterol/fluticasone in combination who had a marginal decrease.[5] BMD at the hip fell by 1.7% for salmeterol patients, whereas it fell by 2.9% and 3.2% in the fluticasone and salmeterol/fluticasone groups, respectively.[5] In contrast, inhaled triamcinolone (not approved for COPD and no longer marketed) was found to lower BMD significantly.[7]

A meta-analysis of observational studies found an increased fracture risk among participants with obstructive lung disease,[8] whereas other trials[5] and their meta-analysis reported no significant effect.[9] Thus, the effect of the currently available ICS on the risk of fractures among patients with COPD remains unclear. Our objective was to ascertain systematically the risk of fractures associated with long-term use of ICS compared with control treatments in both trials and real-world studies in patients with COPD.

METHODS

Inclusion criteria

Our inclusion criteria for RCTs were (1) parallel-group RCT of at least 24 weeks duration; (2) participants with COPD of any severity; (3) fluticasone or budesonide (which are licensed for use in COPD) as the intervention versus a control treatment, in which the comparison groups consisted of ICS versus placebo, or ICS in combination with a LABA versus a LABA alone; and (4) outcome data (including zero events) on fracture adverse events.

We also evaluated controlled observational studies (case–control, prospective cohort or retrospective cohort) reporting on the risk of fractures with any ICS exposure compared with those without ICS exposure in COPD. Eligible studies had to present ORs, RR/HRs or sufficient data to enable us to calculate the OR.

Exclusion criteria

We excluded trials of <24 weeks duration as we were interested in long-term fracture risk. We also excluded studies evaluating ICS use in acute exacerbations of COPD, or where mixed groups of participants (asthma/COPD) were enrolled but fracture outcomes were not separately reported for each group.

Search strategy

An electronic search (MEDLINE and EMBASE) was originally carried out in April 2009 as part of an earlier systematic review,[10] and this search was updated in August 2010 (see the online Appendix 1 for search terms). We examined the websites of the US Food and Drug Administration, and European regulatory authorities, and the manufacturers' clinical trials register of fluticasone[11] and budesonide.[12] The bibliographies of included studies and Cochrane Systematic Reviews were also used to identify relevant articles.

Study selection

Two reviewers (YKL and RC) independently, and in duplicate, scanned all titles and abstracts that indicated the study was an RCT or observational study evaluating the use of ICS in patients with COPD, and further assessed eligibility after retrieving full text versions of potentially relevant articles.

Study characteristics

We used a prespecified protocol to record study characteristics, diagnostic criteria for COPD, dose and frequency of interventions, mean age, sex and spirometric data of participants, and previous ICS use . The design and relevant data sources, duration of follow-up, the number of study participants and their selection criteria were recorded for the observational studies.

Risk of bias assessment

Two reviewers independently assessed the reporting of blinding, allocation concealment, withdrawals and the loss to follow-up in RCTs. In accordance with recommendations on assessing adverse effects, we extracted information on participant selection, ascertainment of exposure and outcomes, and methods of addressing confounding in observational studies.[13] Publication bias was assessed using a funnel plot.

Data extraction

Two reviewers independently extracted data (including zero events) on fractures (where available) from trial listings of 'Adverse Events' or 'Serious Adverse Events' in the results summaries from the clinical trials register and regulatory documents. In order to avoid duplication, we extracted fracture data based on unique study identifiers where listed. Unpublished reports were subsequently matched to journal manuscripts based on sample size, duration and intervention arms, and additional data extracted where necessary. Authors were contacted for data clarification where needed. Any discrepancies were resolved with 100% agreement after rechecking the source papers and further discussion among the three reviewers.

Statistical analysis

We pooled trial data using Review Manager (RevMan) version 5.1.1 (Nordic Cochrane Center, Copenhagen, Denmark) and calculated the Peto OR, using the recommended approach for meta-analysis of rare adverse events. In situations where the fixed effect model is valid, the Peto OR provides the best CI coverage and has greater statistical power in analysing rare events as compared with the random effects model.[14 15] We assessed statistical heterogeneity using the I^2 statistic, with I^2 >50% indicating a substantial level of heterogeneity.[16] If substantial statistical heterogeneity was found, we planned to explore sources of heterogeneity. Predefined sensitivity analyses were performed to check whether different control comparators and alternative statistical models (fixed effect with no continuity correction using StatsDirect software) would substantially change the findings.[14] Posthoc sensitivity analyses were performed based on long-term trials of >12 months duration, and trials with clear reporting of methodological components such as randomisation, blinding and follow-up.

The number needed to harm (NNH) (and 95% CI) with ICS was calculated by applying the OR estimates to the control

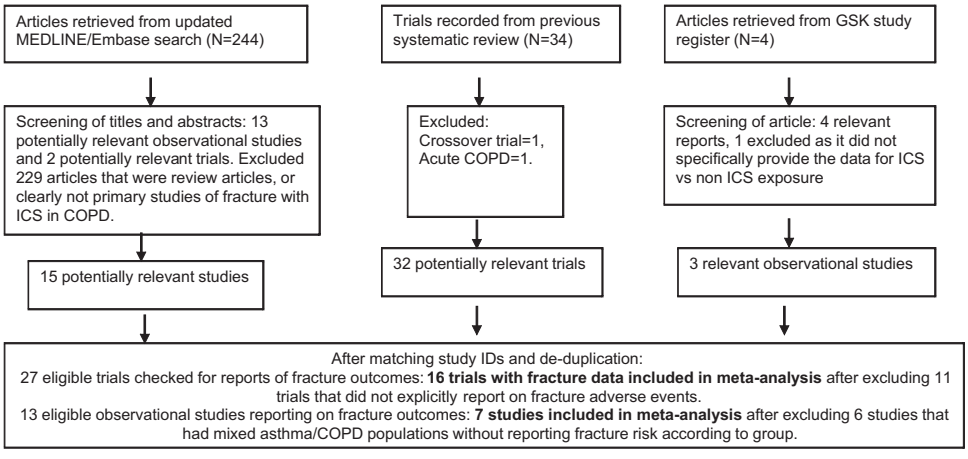


Figure 1 Flow diagram of the process of article selection for meta-analysis. COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids.

Table 1 Characteristics of randomised controlled trials included in the analysis of fractures

Source	Location	Treatment duration, weeks	COPD criteria†‡	Drug	Male, %	Mean age, years (SD)	Mean % predicted FEV_1 (SD)	Prior ICS use (%)
Anzueto SCO100250, 2009[w1 w16]	98 centres in the USA and Canada	52	FEV_1/FVC <70%	SFC 50/250 μg twice daily	51	65.4 (9.1)	34 (11.1)	14
				Sal 50 μg twice daily	57	65.3 (8.8)	33.9 (10.6)	14
Burge FLTB3054, 2000[w2 w17]	18 UK hospitals	156	FEV_1/FVC <70%	Flu 500 μg twice daily	75	63.7 (7.1)	50.3 (14.9)	51.1
				Placebo	74.2	63.8 (7.1)	50.0 (14.9)	57.0
Calverley SFCB3024, 2003[w3 w18]	196 centres in 25 countries	52	ERS	SFC 50/500 μg twice daily	75	62.7 (8.7)	44.8 (14.7)	50
				Sal 50 μg twice daily	70	63.2 (8.6)	44.3 (13.8)	49
				Flu 500 μg twice daily	70	63.5 (8.5)	45 (13.6)	54
				Placebo	75	63.4 (8.6)	44.2 (13.7)	52
Calverley SCO30003, 2007[w4 w19]	44 centres in 42 countries	156	ERS	SFC 50/500 μg twice daily	75	65 (8.3)	44.3 (12.3)	47
				Sal 50 μg	76	65.1 (8.2)	43.6 (12.6)	45
				Flu 500 μg twice daily	75	65 (8.4)	44.1 (12.3)	47
				Placebo	76	65 (8.2)	44.1 (12.3)	51
Ferguson SCO40043, 2008[w5 w20]	94 centres in North America	52	ATS	SFC 50/250 μg twice daily	58	64.9 (9.0)	39.8 (13.9)	15
				Sal 50 μg twice daily	52	65.0 (9.1)	50.6 (15.4)	18
FLTA 3025, 2005[w6]	55 centres in the USA	24	ATS	Flu 500 μg twice daily	66	63.3 (10)	50 (NA)	NA
				Flu 250 μg twice daily	72	65.2 (8.7)	49 (NA)	NA
				Placebo	70	64.8 (9.5)	48 (NA)	NA
Hanania SFCA3007, 2003[w7 w21]	76 centres in the USA	24	ATS	SFC 50/250 μg twice daily	61	63 (NA)	41 (11)	23
				Sal 50 μg twice daily	58	64 (NA)	42(12)	20
				Flu 250 μg twice daily	66	63 (NA)	42 (11)	28
				Placebo	58	65 (NA)	42 (12)	30
Johnell, 2002[6 w22]	39 centres in nine EU countries	156	FEV_1/FVC <70%	Bud 400 μg twice daily	74 (full cohort)	52 (NA)	77 (NA)	NA
				Placebo	72 (full cohort)	52 (NA)	77 (NA)	NA
Kardos SCO30006, 2007[w8 w23]	95 centres in Germany	52	GOLD	SFC 50/500 μg twice daily	74	63.8 (8.3)	40.4 (8.9)	40.6
				Sal 50 μg twice daily	77.6	64 (8.2)	40.3 (8.5)	44.4
Mahler SFCA3006, 2002[w9 w24]	Multicentre USA	24	ATS	SFC 50/500 μg twice daily	62	61.9 (NA)	41 (NA)	28
				Sal 50 μg twice daily	64	63.5 (NA)	40 (NA)	31
				Flu 500 μg twice daily	61	64.4 (NA)	41 (NA)	25
				Placebo	75	64 (NA)	41 (NA)	18
Paggiaro FLIT97, 1998[w10 w25]	13 European centres	24	ERS	Flu 500 μg twice daily	99	62 (NA)	59 (18)	NA
				Placebo	78	64 (NA)	55 (17)	NA
SCO100470, 2006[w11]	135 centres in Europe and Asia-Pacific	24	GOLD	SFC 50/250 μg twice daily	78.3	63.5 (9.3)	1654 (459)*	NA
				Sal 50 μg twice daily	77.2	63.7 (9.0)	1681 (465)*	NA
SCO40041, 2008[w12]	31 centres in the USA	156	$FEV_1/FVC \leq 70\%$	SFC 50/250 μg twice daily	60	65.4 (8.4)	<70%	NA
				Sal 50 μg twice daily	63	65.9 (9.5)	<70%	NA
SFCT 01/SCO30002, 2005[w13]	49 centres in Italy and Poland	52	FEV_1/VC <88%	Flu 500 μg twice daily	84	64.6 (8.7)	NA	NA
				Placebo	80	65.7 (9.0)	NA	NA
Tashkin, 2008[w14]	194 sites in five countries	26	Prebronchodilator FEV_1 <50%, FEV_1/FVC <70%	Bud 320/For 9 μg twice daily	68	63 (9.0)	33.7 (11.8)	NA
				Bud 160/For 9 μg	64	63 (9.0)	34.1 (10.9)	NA
				Bud 160 μg + For 4.5 μg	74	64 (9.0)	33.5 (10.7)	NA
				Bud 160 μg	68	63 (8.8)	33.5 (10.8)	NA
				Form 4.5 μg	66	64 (9.5)	33.6 (11.3)	NA
				Placebo	69	63 (9.6)	34.6 (10.5)	NA
Wouters SCO40002, 2005[w15 w26]	39 centres in The Netherlands	52	FEV_1/VC <88%	SFC 50/500 μg twice daily	73	63 (7.9)	47.4 (13.9)	85
				Sal 50 μg twice daily	75	64 (7.7)	48.2 (12.9)	87

*Reported mean FEV_1 in millilitres as a percentage of predicted unavailable.
†ATS and GOLD criteria for COPD are FEV_1/FVC <70%.
‡ERS criteria for COPD are FEV_1/VC <88% predicted for men and <89% predicted for women.
ATS, American Thoracic Society; Bud, budesonide; COPD, chronic obstructive pulmonary disease; ERS, European Respiratory Society; FEV_1, forced expiratory volume in the first second of expiration; Flu, fluticasone propionate; For, formoterol; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; NA, not available; Sal, salmeterol xinafoate; SFC, combination of salmeterol and fluticasone; VC, vital capacity.

event rate in a large trial population using Visual Rx, version 2.0.[17] Herein, the NNH is the number of patients who need to be treated with ICS for an additional patient to be harmed by a fracture.

ORs from the observational studies were pooled separately from the RCTs, using the inverse variance, fixed effect model. We assumed similarity between the RR and OR because fractures were rare events.[18] We prespecified the choice of data for analysis, starting preferentially with: (1) current and/or recent users' versus remote users or non-users; (2) use within the past 6 months—1 year versus remote users or non-users; and (3) any exposure versus non-exposure. To estimate a dose—response trend as log ORs across different exposure levels, we used inverse variance-weighted least squares regression to pool studies that reported dose-specific risk estimates with one referent category. The adjusted OR and their CIs, and the dose of ICS as beclomethasone equivalents in each exposure level, were abstracted. We estimated the median dose for each exposure level when only dose ranges were available. We assumed that open-ended exposure levels would follow the same range pattern as the previous levels. The dose—response analysis was carried out in Stata 10.0.

RESULTS

The flow chart of study selection is shown in figure 1. A total of 16 RCTs and seven observational studies fulfilled our inclusion criteria for the meta-anaysis.

Table 2 Risk of bias assessment and fracture outcomes in RCTs of inhaled corticosteroids in COPD

Source	Sequence generation	Allocation concealment	AE monitoring*	Drug (n)	Fracture events	Discontinued, n (%)	Loss to follow-up, n (%)
Anzueto SCO100250, 2009[w1 w16]	Adequate, centrally generated block	Adequate	AEs and SAEs recorded after study medication but no later than last date after study medication	SFC (394)	3	125 (32)	6 (1.5)
				Sal (403)	0	156 (39)	12 (3)
Burge FLTB3054, 2000[w2 w17]	Adequate, computer generated	Adequate	AEs and SAEs recorded throughout the study	Flu (n=376)	4	160 (43)	16 (4.3)
				Placebo (n=375)	7	195 (53)	18 (4.9)
Calverley SFCB3024, 2003[w3 w18]	Adequate, computer generated	Adequate	AEs or SAEs occurring during treatment	SFC (358)	3	89 (25)	8 (2.2)
				Sal (372)	0	119 (32)	8 (2.2)
				Flu (374)	2	108 (29)	8 (2.1)
				Placebo (361)	1	140 (39)	6 (1.7)
Calverley SCO30003, 2007[w4 w19]	Adequate, central allocation	Adequate	AEs reviewed at each visit. Prospectively specified data capture for fracture events and site of fracture	SFC (1546)	78	522 (34)	29 (1.9)
				Sal (1542)	61	561 (37)	15 (1.0)
				Flu (1552)	65	587 (38)	24 (1.6)
				Placebo (1544)	57	673 (44)	21 (1.4)
Ferguson SCO40043, 2008[w5 w20]	Unclear	Unclear	AEs collected at start and end	SFC (394)	3	117 (30)	10 (2.5)
				Sal (388)	3	149 (38)	10 (2.6)
FLTA 3025, 2005[w6]	Unclear	Unclear	AEs and SAEs recorded at each visit	Flu (434)	3	147 (34)	NA
				Placebo (206)	0	79 (38)	NA
Hanania SFCA3007, 2003[w7 w21]	Unclear	Unclear	AE reporting at each visit	SFC (178)	1	53 (30)	NA
				Sal (177)	0	57 (32)	NA
				Flu (183)	0	49 (27)	NA
				Placebo (185)	1	59 (32)	NA
Johnell, 2002[6 w22]	Unclear	Unclear	Spine x-rays on 653 patients at beginning and end of trial	Bud (322)	5	NA	0
				Placebo (331)	3	NA	0
Kardos SCO30006, 2007[w8 w23]	Adequate, centrally generated	Adequate	AEs and SAEs recorded during run in and follow-up	SFC (507)	1	99 (20)	4 (0.8)
				Sal (487)	1	103 (21)	3 (0.6)
Mahler SFCA3006, 2002[w9 w24]	Unclear	Unclear	AEs and SAEs documented	SFC (165)	0	52 (32)	NA
				Sal (160)	0	45 (28)	NA
				Flu (168)	1	68 (41)	NA
				Placebo (181)	0	69 (38)	NA
Paggiaro FLIT97, 1998[w10 w25]	Adequate, computer generated	Adequate	AE defined as untoward medical occurrence during treatment	Flu (142)	1	19 (13)	0
				Placebo (139)	0	27 (19)	2 (1.4)
SCO100470, 2006[w11]	Unclear	Unclear	AEs and SAEs recorded at each study visit	SFC (518)	1	59 (11)	NA
				Sal (532)	0	74 (14)	NA
SCO40041, 2008[w12]	Unclear	Unclear	On therapy AEs and SAEs monitored	SFC (92)	1	36 (39)	NA
				Sal (94)	1	39 (42)	NA
SFCT 01/SCO30002, 2005[w13]	Unclear	Unclear	All AEs occurring after subject consent until end of follow-up	Flu (131)	1	34 (26)	NA
				Placebo (125)	0	40 (32)	NA
Tashkin, 2008[w14]	Computer generated in each centre	Unclear	AEs checked at each clinic visit, and during the final follow-up telephone call	Bud/For(845)	1	125 (15)	13 (1.5)
				Bud (275)	1	63 (23)	4 (1.5)
				For (284)	1	61 (22)	1 (0.4)
				Placebo (300)	0	77 (26)	7 (2.3)
Wouters SCO40002, 2005[w15 w26]	Adequate	Adequate	AE collected at start and end of treatment	SFC (189)	5	34 (18)	0
				Sal (184)	5	46 (25)	0

*All RCTs were double-blinded.

AE, adverse event; Bud, budesonide; COPD, chronic obstructive pulmonary disease; Flu, fluticasone propionate; For, formoterol; For/Bud, combination of formoterol and budesonide; NA, not available; RCT, randomised controlled trial; SAE, serious adverse event; Sal, salmeterol xinafoate; SFC, combination of salmeterol and fluticasone.

Randomised controlled trials

Trial characteristics

Characteristics of the included trials are shown in table 1. There were a total of 17 513 participants with COPD, with 9143 on ICS compared with 8370 controls. The duration of the trials ranged from 24 to 156 weeks, with a mean of 90 weeks across studies.[6 w1–w15] (Note that references prefixed with 'w' can be found in the online supplement.)

Inhaled fluticasone was evaluated in 14 trials, while inhaled budesonide was used in two trials.[6 w14] Trials tended to enrol participants with severe COPD, as the mean forced expiratory volume in 1 s (FEV_1) of the participants was <50% for nine of the trials.[w1 w3–w5 w7–9 w14 w15] There was a predominance of men (>50% male participants in every trial), with the mean ages typically in the 60–70 year range. Where reported, prior ICS use was noted in 25–50% of the participants, except for two trials with past ICS exposure for ~20% of patients.[w1 w5]

Trial quality was variable (table 2). All the RCTs had blinding of participants and personnel. Discontinuation rates varied from no withdrawals to 53%, with some evidence of differentially higher losses in placebo arms.[w2 w4] However, many of the patients who discontinued the assigned intervention appeared to remain available for follow-up, as the reported losses only ranged from none to 4.9%. Seven RCTs provided detailed descriptions regarding blinding, adequate sequence generation, allocation concealment and clear reporting of loss to follow-up, and were at low risk of bias.[w1–w4 w8 w10 w15] The remaining nine RCTs were at unclear risk of bias owing to lack of clarity in reporting the methods of randomisation.[6 w5–w7 w9 w11–w14] None of the trials was designed specifically to evaluate fractures, and the data on fractures were extracted from listings of adverse events, except for subsets of participants in two trials where bone outcomes were measured in detail.[5 6] Five trials gave details on systemic corticosteroid use for COPD exacerbations, and four of the trials showed

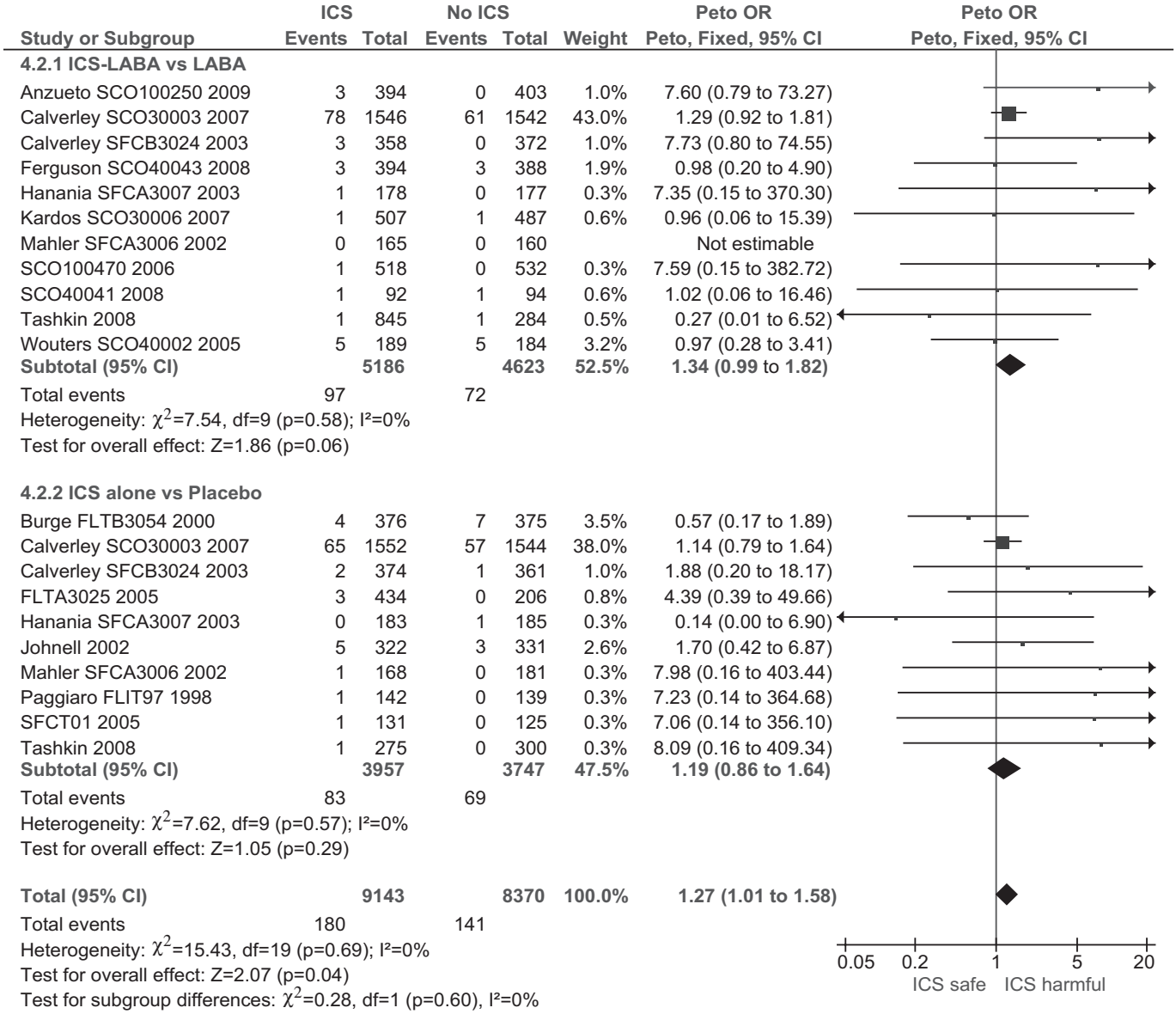


Figure 2 Meta-analysis of odds of fracture with inhaled corticosteroid (ICS) exposure trials of patients with chronic obstructive pulmonary disease. LABA, long-acting β_2-agonist.

a significantly higher use of oral corticosteroid in the non-ICS intervention arms (online table I).

Main findings

Across the mean trial duration of 90 weeks, ICS use was associated with a significant increase in the risk of fractures (180 of 9143 (2.0%) vs 141 of 8370 (1.7%) for control); Peto OR 1.27 (95% CI 1.01 to 1.58; p=0.04) (figure 2). There was no evidence of statistical heterogeneity among the included trials (I^2=0%).

Sensitivity analysis

Fixed effect meta-analysis based on the Mantel–Haenszel model (without a continuity correction) yielded similar findings of an increased OR 1.26 (95% CI 1.01 to 1.59; p=0.04) for fractures in RCTs of ICS in COPD.

The pooled Peto OR for seven trials with complete reporting of quality components was 1.23 (95% CI 0.97 to 1.55),[w1–w4 w8 w10 w15] as compared with a Peto OR of 1.73 (95% CI 0.80 to 3.73) for nine trials where some aspects regarding the process of randomisation were not fully reported.[6 w5–w7 w9 w11–w14]

Restricting the pooled analysis to four long-term trials (each of 156 weeks duration)[6 w2 w4 w12] yielded a pooled OR of 1.19 (95% CI 0.94 to 1.51) that is slightly lower than the overall pooled estimate. This may be due to higher quality studies, or change in risk with time. However, the reliability of fracture estimates from long-terms trials such as TORCH is limited by significantly higher oral corticosteroid exposure (online table 1) and withdrawals (with some crossover to ICS treatment) in the placebo arms.[19]

Publication bias

The funnel plot for fractures appeared to be symmetrical for the RCTs (online figure 1).

Number needed to harm

The NNH for fractures was estimated at 83 (95% CI 38 to 2107) over the 3 year ICS treatment period in the trial, based on the 5.1% fracture rates in the salmeterol and placebo arms for the TORCH trial.[5]

Observational studies

Details of the included studies and the risk of bias are shown in tables 3 and 4.[w27–w33] There were five nested case–control studies,[w28 w29 w31–w33] and two cross-sectional studies.[w27 w30] Three of the studies were based in the USA,[w28–230] while the other four were in Europe.[w27 w31–w33] There was a predominance of females in three studies. Fluticasone and/or budesonide were among the ICS evaluated in all the studies, except for one study that evaluated beclomethasone and triamcinolone.[w30] ICS exposure was estimated from dispensing records, and dosages were usually extrapolated from amounts dispensed. Some patients were identified through diagnostic codes for

Table 3 Characteristics of observational studies of inhaled corticosteroids (ICS) and fractures

Study	Design	Fractures	Data source	COPD definition and patient characteristics	Type of ICS
Gonnelli, 2010[w27]	Cross-sectional	Vertebral	57 Italian outpatient pulmonary centres January–December 2005, 3030 eligible patients	Age >50 years, referred by family physicians for COPD, FEV_1/FVC <70%, with recent lateral CXR. Mean age 70 years, 58% males	BDP, BUD, FP, TRIAM
Johannes, 2005[w28]	Nested CC	Non-vertebral mainly (64%) upper or lower limb fractures	United Healthcare database 1997–2001. 609 cases/6323 controls	Adults aged ≥40 years with ICD-9 codes for COPD and asthma (we used data on patients with COPD only). Mean age 52 years, 30% of cases were male	FP, BDP, BUD, FLUNIS, TRIAM
Lee, 2004[w29]	Nested CC	Non-vertebral	VA patients; 1708 cases/6817 controls	New patients with COPD identified by ICD-9 coding. Mean age 63 years, 95% male, with 1.8 years follow-up	TRIAM, BDP, FLUNIS, FP
McEvoy, 1998[w30]	Cross-sectional	Vertebral	Minneapolis VA 176 users/136 non-users	Selection criteria: (1) male >50 years old; (2) primary diagnosis COPD; (3) FEV_1/FVC ratio 70%; (4) smoking history ≥20 pack-years; and (5) >5 refills of a β-agonist inhaler within past year. Mean age 69 years	BDP, TRIAM
Pujades-Rodríguez, 2007[w31]	Nested CC	Any	UK Health Improvement Network database 1998–2005. 1235 cases/4598 controls	COPD diagnosis based on general practice records. Mean age 69 years, 40% males. Mean predicted FEV_1 of 58%. Controls matched by sex and general practice	BDP, FP, BUD
WEUSRTP1127 Miller, 2010[w32 w34]	Nested CC Non-vertebral fracture	Non-vertebral	UK GPRD 2003–2006, 1523 cases/1876 controls	COPD diagnosis on computerised records. Age ≥45 years, 37% male. Controls matched on age, sex, general practice and duration in cohort prior to index date	Primary analysis FP, incomplete reporting BDP and BUD data
WWE113669, 2008[w33]	Nested CC	Non-vertebral	UK GPRD 1987–2000, 3105 cases/37 801 controls.	COPD diagnosis on computerised records. Age 50–85 years, 66% male. Controls matched on age, sex and general practice	FP, BUD, BDP

BDP, beclomethasone; BUD, budesonide; CC, case–control; COPD, chronic obstructive pulmonary disease; CXR, chest x-ray; FEV_1, forced expiratory volume in the first second of expiration; FLUNIS, flunisolide; FP, fluticasone, FVC, forced vital capacity; GPRD, General Practitioner Research Database; ICD, International Classification of Diseases; TRIAM, triamcinolone; VA, Veterans Affairs.

Table 4 Validity assessment and results of observational studies

Study	Ascertainment of outcome	Ascertainment of exposure	Adjustments	Limitations and bias	ICS exposure (BDP equivalents where available)	OR (95% CI)
Gonnelli, 2010[w27]	Physicians assessed the lateral CXR using MorphoExpress software	Direct interview of patients and checking of medical records	Age, gender, BMI, and COPD severity	Cross-sectional design limits ability to adjust for confounders, or to establish temporal association. Exposure data from patient interviews are subject to recall bias	≤750 μg	1.26 (0.98 to 1.89)
					750–1500 μg	1.36 (0.93 to 1.72)
					>1500 μg	1.40 (1.04 to 1.89)
Johannes, 2005[w28]	ICD-9 codes for non-verterbral fractures, and claims for physician or hospital care	Pharmacy claims for ICS use in the past year prior to fracture	Demographics, medical conditions, medications including oral corticosteroid use, and health utilisation for underlying respiratory disease	No spirometric definition of COPD. Reliance on ICD codes and insurance claims. Relatively few subjects aged ≥65 years. Lack of adjustment for important confounding variables. Funded by manufacturer of ICS	30 days prior vs no current use	0.86 (0.59 to 1.25)
					90 days prior vs no recent use	1.02 (0.77 to 1.36)
					1–167 μg	0.88 (0.64 to 1.19)
					168–504 μg	0.82 (0.54 to 1.26)
					505–840 μg	1.22 (0.67 to 2.25)
					> 840 μg	1.05 (0.53 to 2.07)
Lee, 2004[w29]	ICD-9 codes for non-vertebral fractures. No specific validation for this study	Based on outpatient pharmacy claims database	Co-morbidities, medications, annual hospitalisation and oral corticosteroid use	No spirometric definition for COPD. Reliance on ICD coding, lack of adjustment for potentially important confounders, no lung function data. Funded by manufacturer of ICS	Current user (last 30 days) vs non current	1.20 (0.94 to 1.54)
					Recent user (last 90 days) vs non-recent user	1.14 (0.95 to 1.37)
					ICS <300 μg vs no ICS	0.83 (0.66 to 1.04)
					ICS 300–699 μg vs no ICS	0.96 (0.78 to 1.17)
					ICS >700 μg vs no ICS	1.20 (0.95 to 1.52)
McEvoy, 1998[w30]	Lateral lumbar and thoracic x-rays independently reviewed by blinded radiologists.	Computerised pharmacy records, ICS use ≥4 puffs a day ≥6 months of past year, and no more than 2 brief oral steroid courses.	Smoking history, FEV_1, Baseline Dyspnoea Index, Activity Limitation Score and General Health Status Index	Analysis restricted to male patients >50 years. Cross-sectional design limits the ability to adjust for all confounders	ICS use ≥4 puffs a day for at least 6 months of past year	1.38 (0.71 to 2.69)
Pujades-Rodríguez, 2007[w31]	Any fracture recorded in electronic medical records (13% were hip, and 9% were wrist)	ICS exposure based on electronic prescribing records	Age, predicted FEV_1 and oral corticosteroid use, and matched for sex and general practice	No spirometric definition of COPD. Reliance on general physician record for diagnosis of COPD and outcome/exposure ascertainment	Any ICS use	1.12 (0.97 to 1.29)
					≤100 μg	1.06 (0.88 to 1.28)
					101–200 μg	0.99 (0.78 to 1.27)
					201–400 μg	1.17 (0.95–1.44)
					401–800 μg	1.21 (0.97–1.51)
					801–1600 μg	1.13 (0.87 to 1.46)
					≥1600 μg	1.74 (1.00 to 3.01)
WEUSRTP1127 Miller, 2010[w32 w34]	OxMIS and Read codes for non-vertebral fracture	Based on ICS use in the electronic medical record year prior to index date	COPD hospitalisation, BMI, smoking status, concomitant medication vertebral fractures, co-morbidities	Reliance on electronic medical record coding, lack of adjustment for potentially important confounders, no lung function data. Funded by manufacturer of ICS	Use in past 12 months vs non-use past year	1.25 (1.07 to 1.47)
					Current use (13–25 days) vs non-use in past year	1.10 (0.84 to 1.46)
					Recent use (26–52 days) vs non-use in past year	1.36 (1.04 to 1.77)
					Medium (750 μg) vs none	0.90 (0.67 to 1.20)
					High (1500 μg) vs none	0.92 (0.69 to 1.24)
					Very high (2000 μg) vs none	1.06 (0.68 to 1.66)
WWE113669, 2008[w33]	OxMIS and Read codes for first non-vertebral fracture	Based on ICS use in the electronic medical record 1 year prior to index date	COPD hospitalisation, BMI, smoking status, concomitant medication vertebral fractures, co-morbidities	No spirometric definition of COPD. Reliance on electronic records, no lung function data. Funding source: manufacturer of ICS	Current user (last 30 days) vs non-use past year	1.42 (1.23 to 1.65)
					Recent user (last 31–90 days) vs non-use past year	1.35 (1.16 to 1.58)
					Low dose vs none	1.39 (1.16 to 1.66)
					Medium dose vs none	1.51 (1.24 to 1.83)
					High dose vs none	1.32 (1.13 to 1.55)

BDP, beclomethasone; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CXR, chest x-ray; FEV_1, forced expiratory volume in the first second of expiration; ICD, International Classification of Diseases; OxMIS, Oxford Medical Information Systems.

COPD in electronic databases, and the extent of misclassification is unclear. Four studies were funded by manufacturers of ICS.[w28 w29 w32 w33]

Findings from the meta-analysis of observational studies according to exposure subcategories are shown in figure 3. The pooled estimate based on all seven studies, covering current or ever users versus non-users, showed an OR of 1.21 (95% CI 1.12 to 1.32; p<0.0001, I^2=37%). There were five studies that reported on current users compared with no current exposure which yielded a pooled OR of 1.27 (95% CI 1.14 to 1.41; p<0.0001; I^2=48%).[w28–w30 w32 w33] Four studies reported on recent users compared with no recent exposure, with very similar findings of a pooled OR of 1.24 (95% CI 1.12 to 1.37; p<0.0001; I^2=29%).[w28 w29 w32 w33]

Exclusion of the study that did not enrol fluticasone or budesonide users[w30] did not change the direction or magnitude of the fracture risk for current or ever users (OR 1.21; 95% CI 1.11 to 1.32; p<0.001) in a sensitivity analysis.

One study reported primarily on fluticasone, but provided some data on the category of 'other ICS' exposure involving beclomethasone and budesonide. Meta-analysis based on 'other ICS' category rather than 'fluticasone exposure' yielded a very similar OR of 1.20 (95% CI 1.11 to 1.29).[w32]

Dose–response meta-regression

Six observational studies were included in this analysis.[w27–w29 w31–w33] Each 500 µg increase in beclomethasone dose equivalents was associated with a 9% increase in the likelihood of fractures, OR 1.09 (95% CI 1.06 to 1.12; p<0.001) (figure 4).

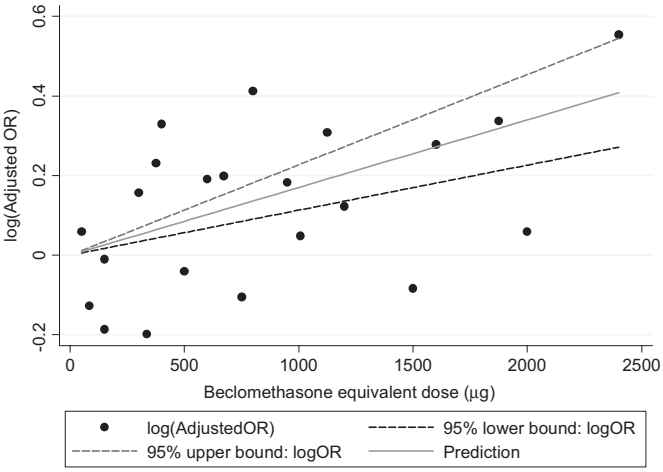


Figure 4 Meta-analysis of inhaled corticosteroids versus controls for fractures in observational studies.

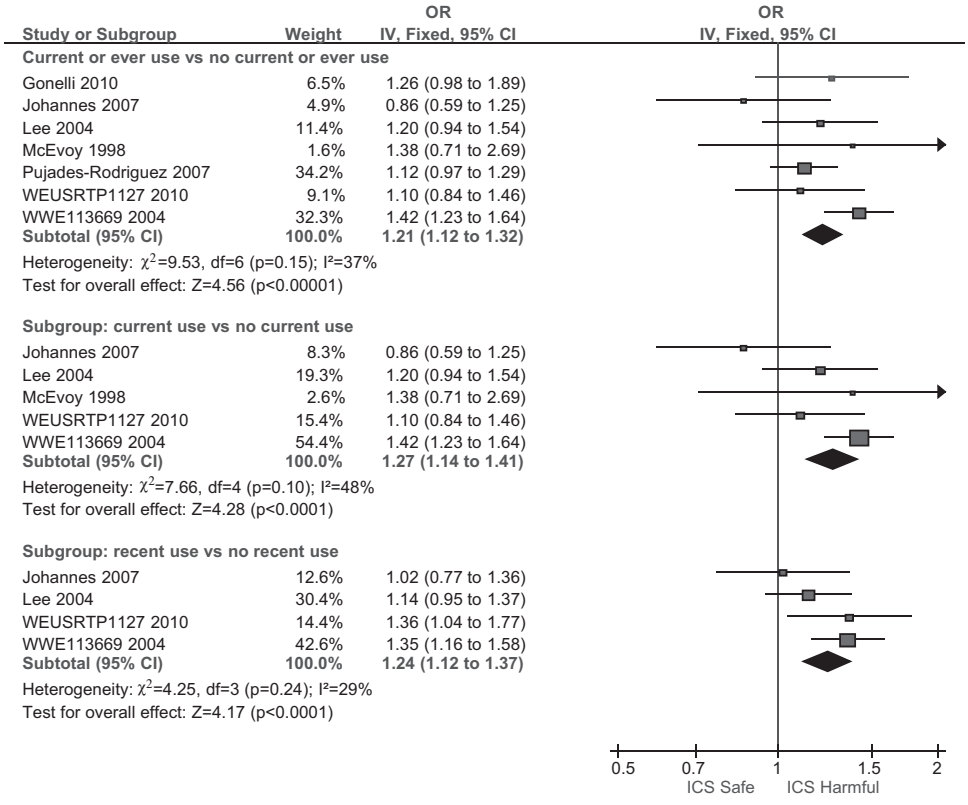
DISCUSSION

Our meta-analysis found consistent evidence on the adverse effects of the available long-term ICS (fluticasone and budesonide) treatment on fractures in patients with COPD. We found a relative increase of >20% in the likelihood of fractures in RCTs and observational studies, Although the pooled estimates from the RCTs are dominated by a single large trial, and the lower bounds of the 95% CIs lie very close to unity, the totality of the evidence should be considered. Here, the consistency and similarity of the point estimates across study designs, the absence of statistical heterogeneity and the presence of a dose–response effect in the observational studies strengthen the confidence in this association.

Comparisons with previous analysis

Our consistent findings from trials and observational studies in COPD should be distinguished from previous underpowered meta-analyses limited to published trials, or observational studies which included patients with conditions other than

Figure 3 Meta-analysis of odds of fracture with subcategories of inhaled corticosteroid exposure in observational studies of patients with chronic obstructive pulmonary disease.



COPD. A meta-analysis of ICS in older adults found no consistent risk based on three COPD trials and several observational studies that enrolled patients who did not have COPD.[20] Similarly, another meta-analysis reported no increase in fractures based on published data from three long-term trials.[9] There are also two Cochrane reviews that reported inconclusive findings on the link between ICS and fractures.[21 22] Another pooled analysis limited to five published case–control studies which included those with other respiratory conditions such as asthma reported a dose-related increased relative fracture risk of 12% per 1000 μg increase in beclomethasone equivalents.[8] In contrast, our comprehensive meta-analysis of clinical trials included unpublished data with sufficient power to reliably detect a relatively precise estimate of the increase in the likelihood of fractures among 17 513 patients with COPD.

The precise mechanisms by which ICS increase the risk of fractures in patients with COPD are uncertain. Patients with COPD are already at high risk from osteoporosis and fractures, which may stem from co-morbidity (eg, susceptibility to falls), nutritional deficiencies, inflammatory markers, and prior corticosteroid exposure.[23] A small portion of the ICS dose is systemically absorbed and systemic effects are recognised. At large doses, the adverse effects of ICS may come close to that of oral corticosteroids, known to cause increased bone resorption and decreased bone formation in a dose-dependent manner consistent with our dose–response analysis.[24]

Limitations

The lower limit of the 95% CI for fracture risk from RCT data is close to the threshold of the null effect, thus introducing an element of uncertainty. Moreover, the trial data originate mainly from unpublished, non-peer-reviewed company reports. Absence of information in RCTs regarding timing of fracture in relation to ICS use also precludes meta-regression of fracture risk according to exposure duration. Most of the RCTs did not use specific methods to define and record fractures, and it is possible that misclassification or underascertainment occurred, although this should not have a differential effect in a double-blind study. Many trial participants had previous ICS exposure prior to joining the trial, and we noted differential oral corticosteroid exposure in control arms (online table 1), thus attenuating observable differences between groups.[19] While risk estimates from observational data were adjusted for concomitant medications, this was not so for the RCTs, and the extent of bisphosphonate use may affect the fracture risk.[5]

Data on budesonide are available from only two trials,[6] and there are no head to head long-term trials of fluticasone versus budesonide in COPD. We did not specifically evaluate trials of flunisolide, triamcinolone or mometasone as they are not licensed for COPD. Most trial participants were male, and studies were based on older ICS devices, limiting applicability. Observational studies are susceptible to residual confounding.

Future research

Future studies should evaluate the precise location of the fractures (peripheral vs central, traumatic vs non-traumatic), and whether the risk varies by COPD severity. Studies should attempt to determine whether concomitant bone-protective drugs can ameliorate this risk of fractures associated with ICS, and should recruit a larger proportion of postmenopausal women. The risk of fractures associated with the newer formulations of ICS needs to be assessed. The dose–response relationships for efficacy and safety need detailed evaluation so that the lowest effective dose can be prescribed.

Implications for clinical practice

The relative increase of ~27% in fracture risk should be weighted against the 20–25% relative reduction of COPD exacerbations, with a potential number needed to treat of 6 per year in preventing exacerbations.[4] This contrasts with the fracture NNH of 83 over a 3-year period in the same trial population. Thus, the benefit/harm ratio may be less of a concern for patients with low underlying fracture risk but who have more severe COPD and are experiencing frequent exacerbations. However, as cumulative ICS exposure may be hazardous in older patients with multiple co-morbidities and low BMD, ICS treatment needs more careful consideration, and bone-protective drugs may be warranted.

Conclusions

Our findings suggest a dose-dependent increased risk of fractures associated with the long-term use of inhaled fluticasone or budesonide in patients with COPD. Clinicians should carefully consider the modest risk of fractures associated with ICS treatment, along with their adverse effects on other outcomes and balance this against the symptomatic benefits in reducing exacerbations.

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Competing interests None.

Contributors YKL and SS conceptualised the review and drew up the protocol. YKL, SS and RC were involved in study selection and data extraction. YKL and RC performed the data analysis. YKL, RC and SS drafted and revised the manuscript.

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