

GSK Medicine: Fluticasone propionate, beclomethasone
Study No.: WWE113669/EPI40204
Title: The use of inhaled corticosteroids and risk of non-vertebral fracture among COPD patients in the UK General Research Practice Database: a nested case-control study
Rationale: Randomized control trials of inhaled corticosteroid (ICS) use among chronic obstructive pulmonary disease (COPD) patients have produced conflicting results regarding the drug effect on bone density. Budesonide and fluticasone propionate (FP) were not associated with any significant effect on bone while triamcinolone was associated with a decrease in bone density. Observational studies suggest a slight increase in risk of fracture with inhaled corticosteroid use, yet these data do not include results for COPD patients separately. In order to better allow physicians and patients to better weigh the increased risk and benefits of these medications for the treatment of COPD, this study aimed to quantify the risks of ICS use on the outcome of non-vertebral fracture in COPD patients.
Objectives: The purpose of the study was to quantify the association between non-vertebral fracture and use of inhaled corticosteroids (ICS) in COPD patients, controlling for oral corticosteroid use and other potential confounding factors. The primary objective of the study was to obtain measures of the association between the outcome non-vertebral fracture and inhaled corticosteroid exposure in a cohort of COPD patients using a nested case control design. The secondary outcomes were to evaluate 1) the risk of fracture by duration of ICS use for the class and each drug separately (fluticasone propionate, budesonide, beclomethasone dipropionate 2) the risk of fracture by ICS dose for the class and each drug separately (fluticasone propionate, budesonide, beclomethasone dipropionate 3) the risk by non-vertebral fracture site (hip, upper limb, lower limb, all) and 4) to produce fracture incidence rates (absolute risk) by ICS use categories.
Indication: Chronic Obstructive Pulmonary Disease
Study Investigators/Centers: GSK conducted study
Research Methods
Data Source: This study was conducted using the General Practice Research Database (GPRD), managed by the Medicines Control Agency in the United Kingdom. The database comprises the entire computerized medical records of a sample of general practitioners (GPs) in the country. All members of the population are registered with a single practice, which centralizes the medical information not only from GPs themselves but also from specialist referrals and hospital attendances. This study is based on data from about a 6% sample of the UK population.
Study Design: A nested case control design within a cohort of COPD patients in the General Practice Research Database was selected. Cases were defined as patients with OXMIS and READ codes consistent with first non-vertebral fracture recorded in their medical records. Controls were defined as patients without any claims for non-vertebral fracture and were selected for each case at a ratio of up to 4:1 from the COPD cohort membership. Controls were matched on sex, age within two years, and practice.
Study Population: The study population was defined as patients with a diagnosis of COPD with and without concomitant asthma from 1987 forward who were ≥ 50 years old at the time of index date and had at least 12 months of eligibility in the GPRD system prior to index date. The index date was defined as the first non-vertebral fracture date for cases or a randomly assigned date for controls. In addition, patients had a COPD diagnosis that was present at least 12 months prior to index date and a COPD-related visit or respiratory drug use that occurred within the 12 months prior to index date. Only data from practices meeting quality-reporting standards were included. Patients were excluded from the cohort if they had 1) a diagnosis of cystic fibrosis or 2) no COPD label (healthcare utilization or respiratory drug use) in the 12 months prior to index date or 3) were < 50 or > 85 years old at the index date or 4) had less than 12 months of data available prior to index date.
Study Exposures, Outcomes: Exposure to inhaled corticosteroids was classified by reviewing all prescriptions dispensed in the time between entry into the cohort and the index date. Exposure was classified as to the recency of exposure prior to the index date (within 30 days, 31-90 days, 91-180 days etc), dose and duration of use for each drug prior to the index date. Cumulative exposure to inhaled corticosteroids was defined as total number of beclomethasone equivalents prior to index date. Duration of exposure was defined as both the total number of ICS scripts and the total numbers of years exposed to ICS, for both the combined class variable and each ICS (BDP, BUD, FP) separately.
Covariate measures included: 1) recent use and duration (number of prescriptions) of OS use in the prior twelve months was calculated 2) respiratory-related hospitalizations measured as part of disease severity 3) age at index event (part of matching criteria) 4) smoking status at index date (current, former, never) 5) body mass index, coded as low, normal (referent group), overweight and obese according to NIH published definitions.

Data Analysis Methods: Fracture incidence rates and 95% confidence intervals by ICS exposure, demographic, other medication use, and comorbid condition categories for the entire COPD cohort were calculated. Fracture rates by ICS use were also presented stratified by age and sex. Crude and adjusted odds ratios with 95% confidence intervals will be estimated for outcomes of all non-vertebral fractures, and for hip and wrist fracture separately. All categorical variables were entered as dummy variables into logistic regression models, to allow for non-linear relationships with increasing levels of a variable value. Exposure to inhaled corticosteroids was modeled as recent use (time windows in year prior to index date), total and past year cumulative exposure (# of scripts, # of days supply, BDP equivalents), and by average daily dose (low, medium, high). In addition to estimating the risk for the ICS drug class, exposure to each individual ICS drug was also evaluated. Conditional logistic regression models were created for matched case and control data to produce adjusted risk (odds ratio) estimates with 95% confidence intervals.

Limitations:

- 1) Confounding by indication as disease severity is associated with both the likelihood of receiving the exposure of interest (ICS) and the probability of the outcome (non-vertebral fracture).
- 2) A lack of direct, standardized clinical measurements when utilizing automated databases like the GPRD. Information about other parameters linked to fracture risk, like physical activity, functional status (performance of activities of daily living), community involvement, and assistance with ambulation, are also absent from electronic medical records and could not be adjusted for in multivariate models.

Study Results

A total number of 3,105 non-vertebral fracture cases and 37,801 potential controls without record of a non-vertebral fracture from the study cohort met all study inclusion and exclusion criteria. Of the cases included in the study, 2029 cases were matched exactly on age, sex, and general practice and 779 matched on sex, general practice, and within one year of age at index date. As many as four matched controls were selected for each case. A total number of 2808 cases and 8453 matched controls were included in the analysis.

Incidence Rates of Fractures:

The overall crude incidence rate of non-vertebral fracture in the COPD cohort was 9.6 per 1,000 person-years. Fracture incidence per 1,000 person-years was higher among women (14.3) than among men (6.1) and increased with age. Inhaled corticosteroid users had a slightly lower crude incidence rate of all fractures (9.5 per 1,000 py) than did nonusers (10.0 per 1,000 py). The crude incidence rate for all non-vertebral fractures among persons ever exposed to BDP, budesonide, or fluticasone were also all lower than the rates among persons never exposed.

Adjusted risk associated with ICS:

Adjusted odds of all non-vertebral fractures associated with any ICS (class) use prior to index date were decreased (OR=0.70, 95%CI: 0.61, 0.79) relative to never users. However, ICS use in the year prior to index date was associated with an increased adjusted risk (OR=1.30, 95%CI: 1.14, 1.47) relative to those without ICS use in the prior year. Current use of BDP (OR=1.46, 95%CI: 1.26, 1.69) or budesonide (OR=1.41, 95%CI: 1.10, 1.79), but not fluticasone propionate (OR =0.78, 95%CI: 0.55, 1.09), was associated with fracture.

Adjusted risk associated with duration of ICS use:

Risk of all non-vertebral fractures associated with duration of ICS use, was increased for the 201-280 days use group relative to no use (OR=1.32, 95%CI: 1.09, 1.59). Recent use of FP, regardless of duration category was not associated with increased risk of fracture. No clear pattern of effect modification of the ICS duration in the prior year and non-vertebral fracture risk association by sex was indicated in stratified models. However, adjusted risks were higher for males versus females for the BDP 7 to 9 prescriptions group (OR=1.90 and OR=1.15, respectively) and for the budesonide 4 to 6 prescriptions group (OR=1.87 and OR=1.16, respectively).

Adjusted risk of non-vertebral fracture associated with average daily ICS dose:

Adjusted risk of fracture with low dose ICS (OR=1.39, 95%CI: 1.16, 1.66) was not different from medium (OR=1.51, 95%CI: 1.24, 1.83) or high doses (OR=1.32, 95%CI: 1.13, 1.55) compared with no use in the year prior to index date.

Adjusted risk of non-vertebral fracture associated with cumulative exposure (BDP equivalents) in the year prior to index date:

No evidence of dose response was observed in multivariate models including dummy variables for four levels of cumulative ICS dose relative to none in the year prior to index date; OR=1.20 (1.03, 1.40) for lowest and OR=1.19 (0.99, 1.44) for highest categories.

Demographics/Baseline Characteristics: Characteristics of COPD Cohort, Cases, and Matched Controls

		Cohort (N)	Cohort (%)	Cases (N)	Cases (%)	Controls (N)	Controls (%)
Age at Entry	Age 50-54	3285	6.8	154	5.5	497	5.9
	Age 55-59	4409	9.1	259	9.2	857	10.1
	Age 60-64	6991	14.5	394	14.0	1497	17.7
	Age 65-69	9284	19.2	536	19.1	1936	22.9
	Age 70-74	9733	20.2	623	22.2	1949	23.1
	Age 75-79	8762	18.1	624	22.2	1365	16.1
	Age 80-85	5830	12.1	218	7.8	352	4.2
Gender	Female	21001	43.5	1746	62.2	4917	58.2
BMI	BMI: < 18.5	2043	4.2	116	4.1	345	4.1
		Cohort (N)	Cohort (%)	Cases (N)	Cases (%)	Controls (N)	Controls (%)
	BMI: 18.5 to 24	11918	24.7	664	23.6	1931	22.8
	BMI: 25 to 29	8835	18.3	522	18.6	1443	17.1

	BMI: 30 or greater	4343	9.0	224	8.0	855	10.1
	BMI: Missing	21155	43.8	1282	45.7	3879	45.9
Smoking Status							
	Non-Smoker	14801	30.6	1004	35.8	2566	30.4
	Current	14026	29.0	854	30.4	2662	31.5
	Ex-smoker	8557	17.7	508	18.1	1534	18.1
	Unknown	10910	22.6	442	15.7	1691	20.0
ICS Use							
	Never	11714	24.3	721	25.7	2399	28.4
	Ever	36580	75.7	2087	74.3	6054	71.6
BDP Use							
	Never	15352	31.8	903	32.2	3012	35.6
	Ever	32942	68.2	1905	67.8	5441	64.4
BUD USE							
	Never	39608	82.0	2335	83.2	7167	84.8
	Ever	8686	18.0	473	16.8	1286	15.2
FP Use							
	Never	44461	92.1	2683	95.5	8010	94.8
	Ever	3833	7.9	125	4.5	443	5.2
OCS Use							
	Never	44969	93.1	2632	93.7	7983	94.4
	Ever	3325	6.9	176	6.3	470	5.6
Comorbidities							
	Vertebral Fracture	641	1.3	93	3.3	87	1.0
	Depression	9334	19.3	720	25.6	1729	20.5
	Diabetes	3269	6.8	197	7.0	584	6.9
	Rheumatoid Arthritis	950	2.0	77	2.7	186	2.2
	Asthma	24684	51.1	1619	57.7	4464	52.8
	Osteoporosis	2091	4.3	239	8.5	404	4.8
	Stroke	3023	6.3	176	6.3	462	5.5
	Anemia	4156	8.6	319	11.4	698	8.3
	Osteopenia	131	0.3	11	0.4	25	0.3
	Back Pain	14120	29.2	1081	38.5	2592	30.7
	Falls	5443	11.3	453	16.1	953	11.3
		Cohort (N)	Cohort (%)	Cases (N)	Cases (%)	Controls (N)	Controls (%)
	Hyperparathyroid	125	0.3	12	0.4	32	0.4
	Dementia	1035	2.1	65	2.3	147	1.7
	Hypertension	10842	22.4	674	24.0	2109	24.9
	Dyslipidemia	1640	3.4	106	3.8	325	3.8
	Obesity	2336	4.8	160	5.7	507	6.0
	Vitamin D Deficiency	30	0.1	5	0.2	5	0.1
Primary and Secondary Outcome(s):							
All NonVertebral Fractures Incidence Per 1000 Person Years: COPD Cohort							
		#of Fractures	Person-Years	Incidence Rate	95% Confidence Interval		
Fracture		3105	324014.8	9.58	(9.25, 9.93)		
Age							

	50-54	239	22065.6	10.83	(9.50, 12.30)
	55-59	300	30086	9.97	(8.87, 11.17)
	60-64	445	47693.1	9.33	(8.48, 10.24)
	65-69	580	63120.6	9.19	(8.46, 9.97)
	70-74	653	64551.6	10.12	(9.35, 10.92)
	75-79	654	58055.7	11.27	(10.42, 12.16)
	80-85	234	38442.2	6.09	(5.33, 6.92)
Gender					
	Female	1960	137008.8	14.31	(13.68, 14.95)
	Male	1145	187006	6.12	(5.77, 6.49)
BMI					
	BMI: < 18.5	132	13177.9	10.02	(8.38, 11.88)
	BMI: 18.5 to 24	754	78645	9.59	(8.92, 10.30)
	BMI: 25 to 29	579	57773.2	10.02	(9.22, 10.87)
	BMI: 30 or greater	249	28334.9	8.79	(7.73, 9.95)
	BMI: Missing	1391	146083.8	9.52	(9.03, 10.04)
Smoking Status					
	Non-Smoker	1114	99767.7	11.17	(10.52, 11.84)
	Current	981	91046.3	10.77	(10.11, 11.47)
	Ex-smoker	548	56171.4	9.76	(8.96, 10.61)
	Unknown	462	77029.5	6.00	(5.46, 6.57)
ICS Use					
	No	788	79031.9	9.97	(9.29, 10.69)
	Yes	2317	244982.9	9.46	(9.08, 9.85)
Beclomethasone Use					
	No	986	100969.7	9.77	(9.17, 10.39)
	Yes	2119	223045.2	9.50	(9.10, 9.91)
Budesonide Use					
	No	2578	265901.3	9.70	(9.32, 10.08)
	Yes	527	58113.5	9.07	(8.31, 9.88)
Fluticasone Use					
	No	2961	298841.8	9.91	(9.55, 10.27)
	Yes	144	25173	5.72	(4.82, 6.73)

Risk of All Non-Vertebral Fractures: Multiple Logistic Regression

Table 15: Recent ICS (Class) Use in Past Year

	Adjusted OR*	95% CI
ICS: No Use in Year	1.00	Reference
ICS: Last Use Prior 30 days	1.42	(1.23, 1.65)
ICS: Last Use Prior 31 - 90 days	1.35	(1.16, 1.58)
ICS: Last Use Prior 91 - 180 days	1.22	(0.99, 1.49)
ICS: Last Use Prior 181 - 365 days	0.93	(0.75, 1.17)
Asthma	0.76	(0.68, 0.85)
Antibiotics: No Scripts in last year	1.00	Reference
Antibiotics: 1 Script in last year	1.45	(1.28, 1.65)
Antibiotics: 2 Scripts in last year	1.57	(1.34, 1.83)

Antibiotics: 3+ Scripts in last year	1.61	(1.41, 1.84)
Bronchodialator: 0-1 Script in last year	1.00	Reference
Bronchodialator: 2-5 scripts in last year	2.14	(1.81, 2.51)
Bronchodialator: 6-10 scripts in last year	2.03	(1.72, 2.39)
Bronchodialator: 11-18 scripts in last year	1.95	(1.65, 2.31)
Bronchodialator: > 18 scripts in last year	2.00	(1.68, 2.38)
OCS: No Scripts in last year	1.00	Reference
OCS: 1-2 script in last year	1.25	(0.83, 1.90)
OCS: 3+ scripts in last year	1.85	(1.13, 3.02)
*Adjusted for: COPD Visits, Hospitalizations, BMI, Smoking Status, Calcitonin Use, Statin Use, Bisphosphonates Use, Anticonvulsant Use, Estrogen Use, Vertebral Fractures, Depression, Diabetes, Rheumatoid Arthritis, Osteoporosis, Osteopenia, Anemia, Back Pain, Falls, Hyperparathyroidism, Dementia, Hypertension, Vitamin D Deficiency		
Note: Controls matched to cases on age, sex, and general practice		
Risk of All Non-Vertebral Fractures: Multiple Logistic Regression		
Recent ICS (BDP,BUD,FP) Use in Past Year		
	Adjusted OR*	95% CI
BDP: No Use in Year	1.00	Reference
BDP: Last Use Prior 30 days	1.46	(1.26, 1.69)
BDP: Last Use Prior 31 - 90 days	1.41	(1.20, 1.64)
BDP: Last Use Prior 91 - 180 days	1.18	(0.96, 1.45)
BDP: Last Use Prior 181 - 365 days	0.99	(0.80, 1.24)
BUD: No Use in Year	1.00	Reference
BUD: Last Use Prior 30 days	1.40	(1.10, 1.79)
BUD: Last Use Prior 31 - 90 days	1.10	(0.82, 1.50)
BUD: Last Use Prior 91 - 180 days	1.33	(0.91, 1.93)
BUD: Last Use Prior 181 - 365 days	0.94	(0.65, 1.37)
FP: No Use in Year	1.00	Reference
FP: Last Use Prior 30 days	0.78	(0.55, 1.09)
FP: Last Use Prior 31 - 90 days	0.69	(0.40, 1.19)
FP: Last Use Prior 91 - 180 days	0.53	(0.21, 1.35)
FP: Last Use Prior 181 - 365 days	0.58	(0.28, 1.21)
Asthma	0.77	(0.69, 0.86)
Antibiotics: No Scripts in last year	1.00	Reference
Antibiotics: 1 Script in last year	1.45	(1.28, 1.65)
Antibiotics: 2 Scripts in last year	1.56	(1.34, 1.82)
Antibiotics: 3+ Scripts in last year	1.61	(1.41, 1.84)
Bronchodialator: 0-1 Script in last year	1.00	Reference
Bronchodialator: 2-5 scripts in last year	2.13	(1.81, 2.51)
Bronchodialator: 6-10 scripts in last year	2.03	(1.72, 2.39)
Bronchodialator: 11-18 scripts in last year	1.97	(1.67, 2.33)
Bronchodialator: > 18 scripts in last year	2.03	(1.70, 2.42)
OCS: No Scripts in last year	1.00	Reference
OCS: 1-2 script in last year	1.26	(0.83, 1.91)
OCS: 3+ scripts in last year	1.87	(1.14, 3.07)
*Adjusted for: COPD Visits, Hospitalizations, BMI, Smoking Status, Calcitonin Use, Statin Use, Bisphosphonates Use, Anticonvulsant Use, Estrogen Use, Vertebral Fractures, Depression, Diabetes, Rheumatoid Arthritis, Osteoporosis, Osteopenia, Anemia, Back Pain, Falls, Hyperparathyroidism, Dementia, Hypertension, Vitamin D Deficiency		
Note: Controls matched to cases on age, sex, and general practice		
Conclusion:		
See publication below		
Publications: Davis KJ, Clark D, Knobil K. Inhaled corticosteroid use and risk of non-vertebral fracture among adults with chronic obstructive lung disease in UK general practice. <i>Chest</i> 2003;124:166S.		

Date updated: 10-Apr-2008