

GSK Medicine: Fluticasone propionate, beclomethasone dipropionate
Study No: WVE113662/EPI40207
Title: Assessment of the Risk of Non-vertebral Fractures Associated with Inhaled Corticosteroid Use in Chronic Obstructive Pulmonary Disease Patients in the VA
Rationale: With increased use of ICS in COPD patients, there is growing concern that ICS users may be at an increased risk for developing osteoporosis and experiencing subsequent fractures. The inhaled form of corticosteroids delivers medication directly to the appropriate site, which is intended to limit the systemic effects of the drugs. However, studies have shown that ICS have negative effects on biochemical markers of bone turnover. Patients with advanced COPD have a number of risk factors, including smoking, vitamin D deficiency, low body mass index, sedentary lifestyle, and the use of systemic corticosteroids that contribute to the development of osteoporosis. As patients with COPD are at an increased baseline risk of fractures, it is important to determine if ICS use modifies the magnitude of the risk.
Objectives: The objective of this study was to characterize the risk of non-vertebral fractures in persons with COPD associated with ICS use in the Veterans Affairs (VA) population.
Indication: COPD
Study Investigators/Centers: GSK Conducted Study
Research Methods:
Study Design: A case-control study, in a cohort of VA patients with a new diagnosis of COPD in FY1999 and receiving their first COPD-related medication during that year, was conducted.
Study Population: Patients with COPD who were receiving care in the VA prior to their COPD diagnosis were identified using FY1998 and FY1999 inpatient and outpatient data. To be included in the cohort patients met the following inclusion criteria: 1) any ICD-9 code for COPD at an inpatient or outpatient encounter during FY1999 2) no ICD-9 code for COPD at an inpatient or outpatient encounter in FY1998 3) at least one VA inpatient or outpatient visit during FY1998 4) no prescription for a medication used to treat COPD in the first 3 months of FY1999 5) no fracture in the first 3 months of FY1999 6) filled at least one prescription for a medication used to treat COPD. Cases were patients from the study cohort with non-vertebral fractures occurring after their initial COPD diagnosis date from the second quarter of FY1999 through FY2002. Controls were selected from the eligible cohort of patients that did not have a non-vertebral fracture during the follow-up period. Controls were individually matched to cases at a 4-to-1 ratio on the date of initial COPD diagnosis
Study Exposures, Outcomes: All ICS prescriptions dispensed between the COPD diagnosis date and the date of their first non-vertebral fracture (index date) were identified for cases and controls. Doses of ICS were converted to beclomethasone equivalents and the cumulative exposure was calculated. The average daily dose of ICS over each patient's study period was calculated and categorized it into low dose (<300 µg per day), medium dose (300 µg . 699 µg per day), and high dose (≥700 µg per day). Exposure was classified as ever/never in addition to the recency of the exposure (≤30 days, ≤90 days) to identify current users versus those that had discontinued use. Patients were also classified according to the specific ICS product used during the follow-up period. Subgroup analyses of the risk of fractures were conducted for each of the specific products. In addition, covariates were measured including exposure to both systemic and topical steroids. Oral corticosteroid use was documented as cumulative dose during follow-up time and presence of a recent steroid prescription (≤60 days prior to index date). In addition, exposure to other non-systemic corticosteroids, including nasal and topical formulations, was documented. Exposure to additional covariates which affect bone density or risk of falls was also measured: anticonvulsants, methotrexate, thiazide diuretics, anxiolytics, antipsychotics, antidepressants, anti-Parkinson medications, hormone replacement therapy, bisphosphonates, and vitamin D. We also determined if patients had at least two visits with an ICD-9 code for medical conditions associated with low bone density, corticosteroid use or falls. Where available, information on race and geographic region of the country (northeast, midwest, south, west) was identified. Healthcare utilization was used as a measure of overall health status and disease severity. To assess COPD severity, we identified the number of hospitalizations and outpatient visits with a diagnosis code for COPD. Length of stay was determined for each COPD hospitalization. Classes of medications identified as respiratory related were short-acting beta-agonists, long-acting beta-agonists, anticholinergics, methylxanthines and combination products.
Data Analysis Methods: All analyses were conducted using STATA version 8 statistical software. We used conditional logistic regression to assess both the unadjusted and the adjusted effect of exposure to ICS on the risk of fracture in patients with COPD. In adjusted analyses, we controlled for the potentially confounding factors of medication exposure and medical conditions that were associated with ICS use or fractures. We also considered proxy measures of comorbidity and COPD severity as potential confounders. In addition to using any non-vertebral fracture as the

outcome, we evaluated the risk by the specific type of fracture (hip, wrist, other). Adjusted risks were evaluated in subgroups by sex, age, specific ICS product, and duration of follow-up.

Limitations: The limitations inherent in the data set were as follows 1) The average follow-up time in cases and controls was around 1.75 years and thus may not be sufficient to adequately assess the impact of long-term exposure to ICS and the risk of fractures in patients with COPD 2) Medications filled outside of the VA system are not captured leading to potential misclassification of the unexposed patients as misclassification of the dose of medication to which patients were exposed

Study Results: A total of 40,157 patients met the inclusion criteria, from which 1708 cases were matched to 6817 controls. Patients were 94% male with an average age was 62.7 years. ICS exposure was 21.4% in cases and 22.1% in controls.

Exposure to ICS during the follow-up period was not associated with an increased risk of fractures (Adjusted OR=0.97; 95% CI, 0.84 to 1.11). However, the OR was increased when considering recency of exposure. Among those exposed to ICS within 30 days of their index date the adjusted OR was 1.20 (95% CI, 0.94 to 1.54). Similar results were found among those exposed within 90 days of their index date (recent users) with an adjusted OR of 1.14 (95% CI, 0.95 to 1.37).

In addition to increases in risk associated with recency of exposure, the risk of nonvertebral fractures was also related to the dose of ICS. Patients receiving the highest average daily dose of 700 µg per day or more were at an increased risk of non-vertebral fracture (OR=1.20; 95% CI, 0.95 to 1.52). The risk of fracture was not increased in patients in the two lowest dose categories (<300 µg per day OR=0.83 [95% CI, 0.66 to 1.04] and 301-699 µg per day OR=0.96 [95% CI, 0.78 to 1.17]).

Further analyses indicated an interaction between current use and average daily dose. Patients classified as current users with exposure to ICS at high daily doses were at the highest risk for non-vertebral fractures (Adjusted OR=1.68; 95% CI, 1.10 to 2.57).

By fracture type, hip fractures show the highest risk for fracture in patients recently exposed to ICS (OR:1.69 95% CI, 0.75-3.85). Findings in the .other. fracture group, which comprised the majority of events, were similar to the overall results (Adjusted OR=1.01; 95%CI, 0.87-1.18). Additional subgroup analyses found similar risks of fractures in males and females and no pattern associated with risk of non-vertebral fracture and age.

Four ICS products were used in the VA during the study period. Triamcinolone and beclomethasone were used by 39.2% (N=735) and 32.5% (N=608) of those exposed to ICS. Flunisolide was used by 19.1% (N=358) and fluticasone by 9.2% (N=172) during the study period. Patients exposed to beclomethasone (adjusted OR=0.89 [95% CI, 0.71 to 1.12]), fluticasone (adjusted OR=0.78 [95% CI, 0.51 to 1.19]), and triamcinolone (adjusted OR=0.92 [95% CI, 0.74 to 1.14]) had no increase in the risk of fractures. However, those exposed to flunisolide had increased risks for each of the categories of exposure that were considered. The adjusted odds ratio in those ever exposed was 1.34 (95% CI, 1.01 to 1.78). Current users of flunisolide had the highest risk of fractures (adjusted OR=1.98 [95% CI, 1.26 to 3.13]), while those that were recent users also had an increased risk of fractures (adjusted OR=1.74 [95% CI, 1.23 to 2.47]).

Restricting the analysis to patients with at least two years or three years of follow up, there was no increased risk in non-vertebral fractures among patients ever exposed compared to the never exposed group (2-year follow-up: adjusted OR=1.03 [95% CI, 0.84 to 1.27]; 3-year follow-up: adjusted OR=1.02 [95% CI, 0.70 to 1.50]). As in the main analysis, an increased risk of non-vertebral fractures was observed in the current users, patients exposed to high daily doses and the combination of current users and high daily doses.

Descriptive information on the cases and controls

	Cases N=1708		Controls For example., exposed, cases, other study group(s)/ subgroup(s) as per design and analysis. N=6817 For example., non-exposed, controls, other comparator group(s)/ subgroup(s) as per design and analysis.	
Age, N (%)				
<40	33	(1.9)	132	(1.9)
40-44	86	(5.0)	344	(5.1)
45-49	168	(9.8)	672	(9.9)
50-54	241	(14.1)	964	(14.1)
55-59	171	(10.0)	684	(10.0)
60-64	186	(10.9)	741	(10.9)
65-69	247	(14.5)	988	(14.5)
70-74	203	(11.9)	807	(11.8)
75-79	244	(14.3)	971	(14.2)

80-84	98	(5.7)	392	(5.8)
85-89	26	(1.5)	104	(1.5)
≥90	5	(0.3)	18	(0.3)
Region of Country, N(%)				
Northeast	248	(14.5)	982	(14.4)
South	638	(37.4)	2819	(41.4)
Midwest	370	(21.7)	1460	(21.4)
West	350	(20.5)	1114	(16.3)
Unknown	102	(6.0)	442	(6.5)
Male, N (%)				
	1612	(94.4)	6448	(94.6)
Days of Follow-up				
Mean (SD)	637.2	(349.4)	635.2	(350.1)
≥730 days, N (%)	695	(40.7)	2745	(40.3)
≥1095 days, N (%)	210	(12.3)	803	(11.8)
Comorbidities, N (%)				
Asthma	338	(19.8)	1303	(19.1)
Osteoporosis	85	(5.0)	187	(2.7)
Osteopenia	11	(0.6)	32	(0.5)
Diabetes	922	(54.0)	3130	(45.9)
Anemia	426	(24.9)	1197	(17.6)
Dementia	92	(5.4)	234	(3.4)
Depression	653	(38.2)	1976	(29.0)
Back pain	603	(35.3)	1879	(27.6)
Arthritis	8	(0.5)	15	(0.2)
IBD	13	(0.8)	51	(0.8)
CHF	523	(30.6)	1836	(26.9)
Seizures	183	(10.7)	448	(6.6)
CVA	201	(11.8)	553	(8.1)
Psychoses	152	(8.9)	396	(5.8)
History of falls	48	(2.8)	61	(0.9)
Medication Use, N (%)				
Methotrexate	19	(1.1)	30	(0.4)
Anxiolytics	390	(22.8)	1184	(17.4)
Anticonvulsants	358	(21.0)	933	(13.7)
Antidepressants	758	(44.4)	2304	(33.8)
Antipsychotics	185	(10.8)	555	(8.1)
Thiazide diuretics	186	(10.9)	776	(11.4)
HRT	37	(2.2)	106	(1.6)
Bisphosphonates	41	(2.4)	106	(1.6)
Vitamin D	10	(0.6)	20	(0.3)
Nasal/Topical Corticosteroids	313	(18.3)	1084	(15.9)
Type of Fracture				
Hip	180	(10.5)		
Wrist	96	(5.6)		
Other	1415	(82.9)		
Risk of non-vertebral fracture by categories of exposure to ICS				

	Cases		Controls		Unadjusted OR [95%CI]		Adjusted OR [95%CI]	
No ICS	1343	(78.6)	5309	(77.9)	1.00	–	1.00	–
ICS Ever	365	(21.4)	1508	(22.1)	0.96	[0.84 to 1.09]	0.97	[0.84 to 1.11]
Current user (ICS in last 30 days)	98	(5.7)	307	(4.5)	1.29	[1.02 to 1.64]	1.20	[0.94 to 1.54]
Recent user (ICS in last 90 days)	193	(11.3)	664	(9.7)	1.18	[1.00 to 1.40]	1.14	[0.95 to 1.37]
Average Daily Dose								
< 300 µg	108	(6.3)	526	(7.7)	0.81	[0.65 to 1.01]	0.83	[0.66 to 1.04]
300 – 699 µg	149	(8.7)	626	(9.2)	0.94	[0.78 to 1.14]	0.96	[0.78 to 1.17]
≥ 700 µg	108	(6.3)	356	(5.2)	1.19	[0.95 to 1.50]	1.20	[0.95 to 1.52]
Recency & Dose of Exposure								
Past user (>30 days), Avg. Daily Dose <700 µg/day	194	(11.4)	925	(13.6)	0.83	[0.70 to 0.98]	0.87	[0.73 to 1.03]
Past user (>30 days), Avg. Daily Dose ≥700 µg/day	73	(4.3)	276	(4.1)	1.05	[0.80 to 1.37]	1.06	[0.80 to 1.40]
Current user (≤30 days), Avg. Daily Dose <700 µg/day	63	(3.7)	227	(3.3)	1.10	[0.83 to 1.47]	1.01	[0.75 to 1.37]
Current user (≤30 days), Avg. Daily Dose ≥700 µg/day	35	(2.1)	80	(1.2)	1.71	[1.14 to 2.56]	1.68	[1.10 to 2.57]

^a Adjusted for asthma, other coexisting illness, concomitant medications, history of seizures and falls, and number of annual hospitalizations

Risk of hip fractures by categories of exposure to ICS

	Cases		Unadjusted OR [95%CI]		Adjusted OR [95%CI]	
No ICS	148	(82.2)	1.00	–	1.00	–
ICS Ever	32	(17.8)	0.72	[0.47 to 1.10]	0.74	[0.46 to 1.19]
Current user (ICS in last 30 days)	12	(6.7)	1.62	[0.80 to 3.29]	1.69	[0.75 to 3.85]
Recent user (ICS in last 90 days)	19	(10.6)	1.09	[0.64 to 1.87]	1.11	[0.61 to 2.02]

Average Daily Dose						
< 300 µg	11	(6.1)	0.61	[0.31 to 1.18]	0.59	[0.28 to 1.23]
300 – 699 µg	17	(9.4)	1.03	[0.58 to 1.80]	1.25	[0.65 to 2.39]
≥ 700 µg	4	(2.2)	0.40	[0.14 to 1.16]	0.32	[0.10 to 1.02]

^a Adjusted for asthma, oral corticosteroids, topical corticosteroids, and number of hospitalizations

Risk of fractures other than hip, wrist and vertebral by categories of exposure to ICS

	Cases		Unadjusted OR [95%CI]		Adjusted OR [95%CI]	
No ICS	1108	(78.3)	1.00	–	1.00	–
ICS Ever	307	(21.7)	0.98	[0.85 to 1.13]	1.01	[0.87 to 1.18]
Current user (ICS in last 30 days)	82	(5.8)	1.33	[1.03 to 1.73]	1.26	[0.96 to 1.65]
Recent user (ICS in last 90 days)	160	(11.3)	1.19	[0.98 to 1.43]	1.17	[0.96 to 1.42]
Average Daily Dose						
< 300 µg	87	(6.2)	0.81	[0.64 to 1.03]	0.84	[0.65 to 1.08]
300 – 699 µg	123	(8.7)	0.94	[0.76 to 1.15]	0.96	[0.77 to 1.20]
≥ 700 µg	97	(6.9)	1.32	[1.03 to 1.67]	1.35	[1.05 to 1.73]

^a Adjusted for asthma, other coexisting illness, concomitant medications, history of seizures and falls, and number of annual hospitalizations

Risk of non-vertebral fracture by categories of exposure to product type

	Unadjusted OR [95%CI]		Adjusted OR [95%CI]	
Beclomethasone				
No ICS	1.00	–	1.00	–
Beclomethasone ever	0.87	[0.70 to 1.09]	0.89	[0.71 to 1.12]
Flunisolide				
No ICS	1.00	–	1.00	–
Flunisolide ever	1.39	[1.07 to 1.80]	1.34	[1.01 to 1.78]
Fluticasone				
No ICS	1.00	–	1.00	–
Fluticasone ever	0.80	[0.53 to 1.20]	0.78	[0.51 to 1.19]

Triamcinolone				
No ICS	1.00	–	1.00	–
Triamcinolone ever	0.88	[0.72 to 1.08]	0.92	[0.74 to 1.14]
^a Adjusted for asthma, other coexisting illness, concomitant medications, history of seizures and falls, and number of annual hospitalizations				
Risk of non-vertebral fracture by categories of exposure to flunisolide				
	Unadjusted OR [95%CI]		Adjusted OR [95%CI]	
No ICS	1.00	–	1.00	–
Flunisolide ever	1.39	[1.07 to 1.80]	1.34	[1.01 to 1.78]
No ICS or past flunisolide user (>30 days)	1.00	–	1.00	–
Current user (flunisolide in last 30 days)	2.05	[1.33 to 3.17]	1.98	[1.26 to 3.13]
No ICS or past flunisolide user (>90 days)	1.00	–	1.00	–
Recent user (flunisolide in last 90 days)	1.80	[1.30 to 2.50]	1.74	[1.23 to 2.47]
^a Adjusted for asthma, other coexisting illness, concomitant medications, history of seizures and falls, and number of annual hospitalizations				
Risk of non-vertebral fractures by categories of exposure in patients with at least two years of follow-up				
	Unadjusted OR [95%CI]		Adjusted OR [95%CI]	
No ICS	1.00	–	1.00	–
ICS Ever	0.99	[0.82 to 1.20]	1.03	[0.84 to 1.27]
^a Data set restricted to patients with at least 730 days of follow-up				
^b Adjusted for asthma, other coexisting illness, concomitant medications, history of seizures and falls, and number of annual hospitalizations				
Risk of non-vertebral fractures by categories of exposure in patients with at least three years of follow-up^a				
	Unadjusted OR [95%CI]		Adjusted OR [95%CI]	
No ICS	1.00	–	1.00	–
ICS Ever	0.92	[0.65 to 1.29]	1.02	[0.70 to 1.50]
^a Data set restricted to patients with at least 1095 days of follow-up				
^b Adjusted for asthma, other coexisting illness, concomitant medications, history of seizures and falls, and number of annual hospitalizations				
Conclusion: See publication below.				
Publications: Lee TA, Weiss KB. Fracture risk associated with inhaled corticosteroid use in chronic obstructive pulmonary disease. <i>Am J Respir Crit Care Med</i> 2004;169:855-859.				

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