

<b>GSK Medicine:</b> Fluticasone propionate, beclomethasone
<b>Study No.:</b> WWE113667/EPI40205
<b>Title:</b> A Case-Control Study of the Exposure-Specific Incidence of Fracture with a Focus on Fluticasone Propionate
<p><b>Rationale:</b></p> <p>Trials of inhaled corticosteroids in COPD patients have shown improvement in lung function, exacerbation rate and health status compared with placebo. These results have led the Global Initiative for Chronic Obstructive Lung Disease (GOLD) to include inhaled corticosteroids in their recent recommendations for the treatment of patients who have moderate to severe COPD and repeated acute exacerbations (<a href="http://www.goldcopd.com">www.goldcopd.com</a>). Because of decreased systemic absorption, inhaled corticosteroids generally have a better safety profile than oral corticosteroids. Yet, some evidence suggests that inhaled corticosteroids are associated with adverse effects on bone density and risk of fracture.</p> <p>Two long-term (three year) randomized controlled trials of inhaled corticosteroids in COPD patients showed conflicting results. The existing evidence does not point to a strong association of inhaled corticosteroids with fracture for short term exposure, but more definitive long-term studies are needed.</p>
<p><b>Objectives:</b></p> <p>The purpose of this nested case-control study was to determine the risk of corticosteroid therapies - inhaled and oral on the incidence of treated non-vertebral fracture among patients with medical claims evidence of underlying respiratory disease (asthma and COPD) identified from a large medical claims database.</p> <ol style="list-style-type: none"> <li>1) Identify cases of non-vertebral fracture and suitable controls among eligible United Healthcare members.</li> <li>2) Classify exposure in relation to date of fracture (or randomly chosen index date for controls) according to inhaled corticosteroid use as a class, and separating fluticasone from other inhaled corticosteroids. Further classify exposure with respect to age, oral corticosteroid use, and severity of the underlying COPD or asthma, and other potential risk factors for fracture.</li> <li>3) Provide estimates of the absolute and relative incidence rate of fracture according to exposure status (use of inhaled corticosteroids or other fracture risk factors), and develop appropriate confidence limits for these estimates. Provide stratified incidence rate estimates by type of fracture.</li> </ol>
<b>Indication:</b> COPD
<p><b>Study Investigators/Centers:</b></p> <p>Ingenix Epidemiology Division, A UnitedHealth Group Company</p>
<b>Research Methods</b>
<p><u>Data Source:</u></p> <p>The Ingenix Research Database, which is derived from comprehensive administrative databases of United Healthcare, was used as the source population. The database contains enrollment information documenting patient age, sex, and dates of enrollment as well as medical claims flow into the database from all health care sites (inpatient hospital, outpatient hospital, emergency room, physician's office, surgery center, etc.). Data is obtained from 25 affiliated health plans located in the Northeast, Southeast, Midwest, and Western United States. In addition the database contains pharmacy claims information including drug name, dosage form, drug strength, fill date, days of supply, financial information, and patient and prescriber identifiers, allowing for patient specific longitudinal tracking of medication refill patterns and changes in medications. The data in the Research Database undergo audits by United Healthcare and by Ingenix Epidemiology Division. The validity of the United Healthcare claims has also been documented through review of medical records.</p>
<p><u>Study Design:</u></p> <p>This was a nested case-control study conducted within a fully enumerated cohort of managed care enrollees with health insurance claims indicating the presence of asthma or COPD. Cohort enumeration was accomplished by screening all United Healthcare members aged 40 or older in the Research Database with at least 12 months of continuous membership for the presence of medical claims with ICD-9 diagnosis codes indicating the presence of asthma or COPD. Cases were all persons with claims evidence of an incident fracture occurring during the study period. Controls were randomly selected in a ratio of 10 controls per case from the person-time giving rise to the cases and assigned a random index date. Exposure status was ascertained in the 12 months preceding the index date of fracture or randomly assigned control index date.</p>
<p><u>Study Population</u></p> <p>Members of the respiratory cohort (asthma and/or COPD), were United Healthcare plan members enrolled for at least 12 continuous months and were at least 40 years of age at the time they met their medical claims definition of asthma or COPD (cohort eligibility date). A member met the claims definition of asthma or COPD when there was evidence of at least two outpatient physician visits within a 12 month period, or one inpatient physician visit with claims related to asthma (ICD-9 493.xx) or COPD (ICD-9 491.xx, 492.xx, or 496.xx). Eligibility criteria included: 1) complete medical</p>

coverage and pharmacy benefits 2) enrollment in the health plan for at least 12 continuous months 3)  $\geq 40$  years old. All treated non-vertebral fractures occurring between 1/1/1997 and 6/31/2001 were identified. Fractures that did not represent the first fracture after the cohort eligibility, fractures in the year before the cohort eligibility date, and those with a malignancy other than non-melanoma skin cancer were excluded. The latter two of these exclusion criteria were also applied to the selection of controls.

**Study Exposures, Outcomes:**

A total of 89,877 persons met the respiratory disease cohort definition with 1,722 treated non-vertebral fractures. Exposures and covariates were evaluated in relation to the case or control index date. Covariates were measured in the 365 days before the index date.

Inhaled corticosteroid medications were identified by individual NDC codes within generic name categories. Exposure to inhaled corticosteroids was assessed in the 365 days before the index date for cases and controls. For the purpose of analyses, all inhaled corticosteroids were grouped together as a class, then separate variables were made for those containing fluticasone propionate, alone or in combination with salmeterol, and all types other than fluticasone-containing inhaled corticosteroids were grouped together into another variable. Nasal corticosteroids were grouped together as one covariate. Oral corticosteroids were also identified on the basis of NDC codes and the exposure variables were constructed in the same manner as for the inhaled corticosteroids.

Cases and controls were classified according to the following covariates: 1) demographic factors 2) co-existing medical conditions (vertebral fracture, inactivity, associated corticosteroid use and osteoporosis, disorders of bone, anemia, depression, back pain) 3) dispensing of medication known to affect bone density 4) medical care utilization variables possibly related to fracture 5) exposure to nasal corticosteroids 6) measures of intensity of health care utilization in connection with asthma/COPD

These conditions were defined using claims-based criteria of ICD-9 diagnosis codes and/or procedure or pharmacy codes occurring any time during the year before the index date. In general, definition required at least two outpatient physician visits on separate dates or at least one inpatient visit with the diagnosis codes.

**Data Analysis Methods:**

All analyses were conducted using SAS, version 8.01.

Odds ratios with corresponding 95% confidence intervals for each non-demographic covariate (coexisting medical conditions, medication use, and intensity of medical care utilization in the year before the index date) were estimated individually by multiple logistic regression with fracture as the outcome, adjusting for age at index date, gender, geographic region of health plan, year of cohort eligibility, and season at index date. Crude, stratified and exposure specific incidence rates were calculated with the numerator as the number of all cases, strata specific cases, or exposed cases respectively, and the denominator as the proportion of crude, strata specific or exposed controls multiplied by the total person-time at risk. Ninety-five percent confidence limits were estimated according to the Byar method of Poisson approximation.

Individual odds ratios estimating the risk of fracture with each corticosteroid use group in the separate time windows before the index date were calculated and adjusted for age, gender, season at index date, geographic region, and calendar year of cohort eligibility. Demographically adjusted odds ratios estimating the risk of fracture by cumulative corticosteroid dose during one year, six month, and seven to twelve months before the index date were calculated. Multiple logistic regression models to examine the association of inhaled and oral corticosteroids with risk of fracture were calculated for the entire study population (n=18,942), for the subset of members aged 60 and older (n=4,409), for the subset of the population enrolled consecutively for three or more years (n=7,320), and stratified by underlying respiratory disease (COPD n=6,932 or asthma n=11,277).

**Limitations:** There were several study limitations inherent to the data source: 1) the dose of inhaled corticosteroids was estimated based on the container size and number of containers dispensed 2) fracture diagnosis was not confirmed by medical record review. However a strict definition of fracture, ICD-9 diagnosis code accompanied by a physician or hospital visit with a treatment code in the same claims sequence, was used 3) lifestyle factors that are important contributors to bone mass (BMI, exercise and diet) were not directly measured, but we had good proxy measures of underlying disease severity and medical conditions that predispose to inactivity 4) older persons (age 65 and older) were underrepresented therefore too few hip fractures were ascertained to conduct separate analyses of this fracture type to determine whether the risk for hip fracture is greater following corticosteroid exposure than for other fracture types 5) the population – being enrollees in a managed care organization – are for the large part employed persons and the demographics reflect this. Accordingly, these results might not be generalizable to a more elderly population or to a population without workplace

**Study Results:**

The overall crude incidence rate of treated non-vertebral fracture in the respiratory cohort was 113 fractures per 10,000 person-years. Fracture incidence was higher among females (135 per 10,000 py) than males (81 per 10,000 py), yielding an incidence rate ratio of 1.7.

Inhaled corticosteroid users had a somewhat higher crude incidence rate of fracture (116 per 10,000 py) than did nonusers (111 per 10,000 py), for an incidence rate ratio of 1.05. The crude incidence rate for all non-vertebral fractures among persons exposed to fluticasone in the year before the index date was 121 per 10,000 py, compared to 111 per 10,000 py among those not exposed, for an incidence rate ratio of 1.09, and the IRR for other inhaled corticosteroids was 1.00. The incidence rates for oral corticosteroid use versus nonuse were 121 per 10,000 py and 110 per 10,000 py, respectively, for an incidence rate ratio of 1.10.

There was no indication of an increased risk of fracture among persons with any exposure to inhaled corticosteroids as a class in the year before the index date (OR=1.01, 95% CI: 0.91-1.12), or to fluticasone alone (OR=1.08, 95% CI: 0.94-1.23), inhaled corticosteroids other than fluticasone (OR=0.96, 95% CI: 0.85-1.09), or oral corticosteroids (OR=1.07, 95% CI: 0.96-1.19).

Examining the individual time windows of exposure suggested a small increased risk for those with recent (0-30 days) exposure to inhaled corticosteroids as a class (OR=1.13), particularly fluticasone (OR=1.21), but the confidence intervals included one. No significantly increased risk was seen in any of the other individual time windows (31-90, 91-180, 181-270, or 271-365 days) for inhaled corticosteroids. Oral corticosteroid exposure three to six months before the index date was associated with a 20 percent increased risk of fracture (OR=1.20, 95% CI: 1.02-1.42), but the risk was not substantially elevated or decreased in the other time windows

There were no consistent trends for increasing dose of inhaled or oral corticosteroids and increased fracture risk. In addition, there was no consistent evidence for effect modification by oral corticosteroid use on the relation between inhaled corticosteroids and fracture risk.

Across age categories within dose strata, the risk of fracture with all inhaled steroids as a class does not consistently increase with age except within the highest dose category.

<b>Characteristics of the Respiratory Cohort</b>						
	N	%				
All	89877					
Age						
40-49	35220	39.2				
50-59	33422	37.2				
60-64	12384	13.8				
65-69	4218	4.7				
70-74	2464	2.7				
75+	2169	2.4				
Gender						
Male	37234	41.4				
Qualifying Disease at Cohort Eligibility						
COPD	36190	40.3				
Asthma	50313	56.0				
COPD and Asthma	3374	3.7				
<b>Crude Incidence rates of non-vertebral fracture in patients with medical claims evidence of COPD and Asthma</b>						
By corticosteroid exposure in year before index date						
	Number of Controls	Proportion of Controls	Person Years	Number of Cases	Incidence Rate per 10,000 person years	95% CI
All fractures						

All inhaled							
	Exposed	5979	0.35	53,077	616	116	107-126
	Unexposed	11241	0.65	99,789	1106	111	104-118
Fluticasone							
	Exposed	2609	0.15	23,161	280	121	107-136
	Unexposed	14611	0.85	129,706	1442	111	106-117
Inhaled other than Fluticasone							
	Exposed	3804	0.22	33,769	380	113	102-124
	Unexposed	13416	0.78	119,097	1342	113	107-119
Oral							
	Exposed	4565	0.27	40,525	489	121	110-132
	Unexposed	12655	0.73	112,342	1233	110	104-116

Person-years for strata = proportion in controls times total person-years

#### Timing of Inhaled Corticosteroids and Risk of Nonvertebral Fracture

Characteristic	Cases		Controls		Individual Adjusted Odds Ratio <sup>1</sup>	95% CI	Multiple Adjusted OR	95% CI
	N	%	N	%				
All Inhaled Corticosteroids								
No Exposure	1016	64.2	11,241	65.3	ref		ref	
0-30 days	205	11.9	1902	11.0	1.07	0.92-1.25	1.13	0.94-1.36
31-90 days	312	18.1	3045	17.7	1.01	0.89-1.15	1.04	0.88-1.23
91-180 days	347	20.2	3503	20.3	0.96	0.85-1.09	0.93	0.78-1.10
181-270 days	341	19.8	3385	19.7	0.99	0.87-1.12	1.01	0.85-1.20
271-365 days	336	19.5	3399	19.7	0.96	0.85-1.09	0.94	0.79-1.10
0-90 days	381	22.1	3,692	21.4	1.02	0.90-1.15	1.08	0.92-1.26
91-180 days	347	20.2	3503	20.3	0.96	0.85-1.09	0.94	0.80-1.11
181-365 days	347	26.0	4,468	25.9	0.97	0.87-1.09	0.96	0.83-1.12
Any exposure in year prior	616	35.8	5,979	34.7	1.01	0.91-1.12	n/a	
Fluticasone								
No Exposure	1,442	83.7	14,611	84.8	ref		ref	
0-30 days	105	6.1	888	5.2	1.20	0.97-1.47	1.21	0.93-1.56
31-90 days	138	8.0	1,355	7.9	1.02	0.85-1.06	0.89	0.69-1.13
91-180 days	160	9.3	1,454	8.4	1.10	0.93-1.31	1.07	0.83-1.38
181-270 days	140	8.1	1,308	7.6	1.07	0.89-1.29	0.99	0.76-1.29

271-365 days	134	7.8	1,219	7.1	1.10	0.91-1.33	1.05	0.82-1.35
0-90 days	173	10.0	1,679	9.8	1.03	0.87-1.22	0.93	0.75-1.17
91-180 days	160	9.3	1,454	8.4	1.01	0.93-1.31	1.09	0.86-1.39
181-365 days	187	10.9	1,706	9.9	1.10	0.94-1.30	1.09	0.88-1.34
Any exposure in year prior	280	16.3	2,609	15.2	1.08	0.94-1.23	n/a	
Other Inhaled Exposure <sup>3</sup>								
No Exposure	1,342	77.9	13,416	77.9	ref		ref	
0-30 days	101	5.9	1,022	5.9	0.97	0.78-1.20	1.05	0.81-1.35
31-90 days	178	10.3	1,717	10.0	1.02	0.86-1.20	1.21	0.97-1.5
91-180 days	189	11.0	2,115	12.3	0.85	0.73-1.00	0.80	0.64-0.99
181-270 days	205	11.9	2,120	12.3	0.94	0.80-1.09	1.03	0.83-1.27
271-365 days	208	12.1	2,248	13.1	0.88	0.76-1.03	0.89	0.72-1.09
0-90 days	217	12.3	2,072	12.0	1.03	0.88-1.20	1.24	1.02-1.51
91-180 days	189	11.0	2,115	12.3	0.85	0.73-1.00	0.78	0.63-0.97
181-365 days	280	16.3	2,922	17.0	0.92	0.80-1.05	0.93	0.78-1.11
Any exposure in year prior	380	22.1	3,804	22.1	0.96	0.85-1.09	n/a	
Oral Corticosteroid Exposure								
No Exposure	1,233	71.6	12,655	73.5	Ref		ref	
0-30 days	81	4.7	752	4.4	1.05	0.88-1.33	0.94	0.73-1.21
31-90 days	153	8.9	1,385	8.0	1.09	0.92-1.3	1.00	0.83-1.22
91-180 days	218	12.7	1,782	10.4	1.22	1.05-1.42	1.20	1.02-1.42
181-270 days	188	10.9	1,745	10.1	1.05	0.9-1.24	0.95	0.79-1.13
271-365 days	212	12.3	1,755	10.2	1.21	1.01-1.41	1.18	0.99-1.4
0-90 days	195	11.3	1,797	10.4	1.07	0.92-1.26	0.99	0.84-1.18
91-180 days	218	12.7	1,782	10.2	1.22	1.05-1.42	1.20	1.02-1.42
181-365 days	314	18.2	2,843	16.5	1.10	0.96-1.25	1.05	0.91-1.2
Any Exposure in year prior	489	26.4	4,565	26.5	1.07	0.96-1.19	n/a	

<sup>1</sup>Odds Ratios Adjusted for Age, Gender, Season, Geographic Season, and Calendar Year of Cohort Eligibility, each time window modelled separately

<sup>2</sup>Odds Ratios Adjusted for Age, Gender, Season, Geographic Season, and Calendar Year of Cohort Eligibility, all other time windows(one regression model)

<sup>3</sup>Beclamethasone, Budesonide, Flunisolide, Triamcinolone

**Cumulative Dose of Corticosteroids<sup>1</sup> and Risk of Non-Vertebral Fracture in Time Periods Prior to Index Date**

Type of Corticosteroid	Cases		Controls		Adjusted OR <sup>2</sup>	95%CI
	N	%	N	%		
Year Prior						
All Inhaled						

None	1106	642	11,241	65.3	ref	
<168µg	328	19.0	3202	18.6	1.00	0.87-1.13
168-504µg	183	10.6	1879	10.9	0.96	0.82-1.13
504-840µg	61	3.5	485	2.8	1.24	0.95-1.64
>840µg	44	2.6	413	2.4	1.06	0.77-1.45
Fluticasone						
None	1442	83.7	14,611	84.8	ref	
<168µg	121	7.0	1211	7.0	0.98	0.80-1.19
168-504µg	85	4.9	739	4.3	1.16	0.92-1.46
504-840µg	38	2.2	310	1.8	1.23	0.87-1.73
>840µg	36	2.1	349	2.0	1.03	0.73-1.46
All Oral						
None	1235	71.8	12,661	73.5		
0-30mg	151	8.8	1374	8.0	1.10	0.93-1.31
31-60mg	164	9.5	1533	8.9	1.06	0.90-1.86
61+	172	10.0	1652	9.6	1.03	0.87-1.22
<sup>1</sup> Inhaled dose standardized to beclomethasone, avg daily dose categories for time window						
<sup>2</sup> Odds Ratio, adjusted for Age, gender, Season, geographic region, and calendar year of cohort eligibility						
<b>Risk of Inhaled Corticosteroid Cumulative Dose and Fracture Stratified by Oral Corticosteroid Exposure</b>						
	Cases		Controls			
Characteristic	N	%	N	%	Adjusted OR <sup>1</sup>	95%CI
No Oral Corticosteroid Use in Year Prior to Index Date						
Year Prior						
All Inhaled avg daily dose						
<168µg	199	11.6	1960	11.4	1.01	0.86-1.19
168-504µg	104	6.0	1084	6.3	0.97	0.78-1.20
504-840µg	28	1.6	271	1.6	1.05	0.70-1.56
>840µg	18	1.0	190	1.1	0.98	0.60-1.59
Any Oral Corticosteroid Use in Year Prior to Index Date						
Year Prior						
All Inhaled avg daily dose						
<168µg	129	7.5	1242	7.2	0.96	0.76-1.20
168-504µg	79	4.6	795	4.6	0.95	0.72-1.24
504-840µg	33	1.9	214	1.2	1.48	1.00-2.20
>840µg	26	1.5	223	1.3	1.10	0.72-1.70
<sup>1</sup> Odds Ratio, adjusted for Age, gender, Season, geographic region, and calendar year of cohort eligibility						
<b>Comparisons of Odds Ratios for Entire Study Sample with Age Stratified Odds Ratios</b>						
Dose Category	Entire Sample-OR		OR:40-49		Age Category OR: 50-59	OR: 60+
Year Prior						
All Inhaled avg daily dose						
<168µg	1.00		0.92		1.22	0.85
168-504µg	0.96		1.11		1.16	0.54
504-840µg	1.24		1.45		1.18	1.07
>840µg	1.06		0.66		0.89	1.56
Fluticasone avg daily dose						
<168µg	0.98		0.86		1.04	1.17
168-504µg	1.16		1.02		1.53	0.74
504-840µg	1.23		0.99		1.19	1.60

>840µg	1.03	0.48	0.85	1.87
Other Inhaled avg daily dose				
<168µg	0.99	1.01	1.17	0.69
168-504µg	0.98	1.27	1.10	0.52
504-840µg	1.51	2.82	1.19	0.90
>840µg	1.09	1.53	1.28	0.53
<b>Conclusion:</b> See publication below				
<b>Publications:</b> Johannes CB, Schneider GA, Dube TJ, Alfredson TD, Davis KJ, Walker AM. The risk of nonvertebral fracture related to inhaled corticosteroid exposure among adults with chronic respiratory disease. <i>Chest</i> 2005;127: 89-97.				

Date updated: 10-Apr-2008