AJRCCM Articles in Press. Published on January 7, 2004 as doi:10.1164/rccm.200307-926OC

Fracture Risk Associated with Inhaled Corticosteroid Use in Chronic Obstructive Pulmonary Disease

Todd A. Lee[a,b,c], Kevin B. Weiss[a,b]

[a]Midwest Center for Health Services and Policy Research, Hines VA Hospital, Hines, IL; [b]Center for Healthcare Studies, Division of General Internal Medicine, and the Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL; [c]Department of Pharmacy Practice, College of Pharmacy, University of Illinois at Chicago, Chicago, IL

Corresponding Author:

Todd A. Lee

Midwest Center for Health Services and Policy Research

Hines VA Hospital

PO Box 5000 (151-H)

Hines, IL USA 60141

Phone: 708-202-5869

Fax: 708-202-2316

E-mail: lee@research.hines.med.va.gov

Support: This research was supported by a research grant from GlaxoSmithKline, Research Triangle Park, NC, USA. The investigators worked

independent of the study sponsor in the design and analysis of the study and reporting of the results.

Running Title: Inhaled corticosteroids and fractures

Descriptor Number: 55

Word Count: 2953

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

Abstract

Patients with COPD are frequently treated with inhaled corticosteroids. However, the impact of inhaled corticosteroid use on fracture risk remains unclear in these patients. This nested case-control study examines the association between inhaled corticosteroid use and non-vertebral fractures in Veterans Affairs patients with COPD. From a cohort of 40,157 patients with a COPD diagnosis between October 1, 1998 and September 30, 1999 and that used services in the preceding 12-month period but did not have a COPD diagnosis, 1708 cases with non-vertebral fractures were identified and matched to 6817 controls. Patients were 94% male and average age was 62.7 years. Inhaled corticosteroid exposure was identified through prescription records and converted to beclamethasone equivalents. In conditional logistic regression models, exposure to inhaled corticosteroids at any time during follow-up was not associated with an increased fracture risk (Adjusted Odds Ratio=0.97; 95% CI, 0.84 to 1.11). However, current high dose inhaled corticosteroid users (≥700 μg per day) had an increased risk of fractures compared to patients with no exposure (Adjusted Odds Ratio=1.68; 95% CI, 1.10 to 2.57). In patients with COPD, current use of high dose inhaled corticosteroids was associated with an increased risk of non-vertebral fractures.

Abstract Word Count: 194

Key Words: inhaled corticosteroids; pharmacoepidemiology; chronic obstructive pulmonary disease; nested case-control studies; fractures

Introduction (Word count=336)

The role of inhaled corticosteroids in the treatment of chronic obstructive pulmonary disease (COPD) continues to evolve. A large proportion of patients with COPD are being treated with inhaled corticosteroids.(1) Guidelines for the pharmacological management of COPD recommend inhaled corticosteroids for patients with moderate to severe disease that have a symptomatic or physiologic response to a trial of the medications.(2-7) Concomitant with the increased use of inhaled corticosteriods in patients with COPD, there is concern that users may be at an increased risk for fractures due to the harmful effects of steroids on bone. Systemic corticosteroids have long been linked to decreases in bone mineral density, and a recent epidemiological study showed an association between systemic corticosteroids and fractures.(8)

The inhaled form is intended to deliver medication directly to the site of action and limit the systemic effects of the drugs. However, studies have shown that inhaled corticosteroids have negative effects on biochemical markers of bone turnover.(9) Studies of the association between inhaled corticosteroids and fractures have been less conclusive – showing both an increased risk (10, 11) and no risk (12, 13) associated with inhaled corticosteroid use and fractures. These analyses did not focus solely on patients with COPD.

Assessing the risk of fractures in inhaled corticosteroid users with COPD is particularly important because these patients are at an increased risk of fractures

independent of their use of inhaled corticosteroids.(14-16) Patients with COPD may have a number of risk factors, including a history of smoking, sedentary lifestyle and systemic corticosteroid use, that contribute to the development of osteoporosis, thereby increasing their risk of fractures. Because patients with COPD are at an increased risk of fractures, it is important to determine if inhaled corticosteroid use modifies the magnitude of the risk. The purpose of this study is to examine the association between non-vertebral fractures in persons with COPD and the use of inhaled corticosteroids in the Veterans Affairs (VA) population. Some of the results of this study have been previously reported in the form of abstracts.(17, 18)

Methods (Word count=495)

We conducted a nested case-control study in a cohort of VA patients with COPD. VA inpatient, outpatient, pharmacy, and beneficiary databases were used (see online data supplement for details). The research was approved by the institutional review boards of the Hines VA Hospital and Northwestern University.

Patients were included in the cohort if they had a new diagnosis of COPD (491.x, 492.x, 496) between October 1, 1998 and September 30, 1999, did not fill a respiratory-related medication (Table E1 in online data supplement) or have a fracture in the 90 days following October 1, 1998, and filled at least one

prescription for a respiratory-related medication during their follow-up period. See the online data supplement for additional details on cohort eligibility.

Cases were patients with diagnosis or procedure codes for non-vertebral fractures (Table E2 in online data supplement) occurring after their initial COPD diagnosis date and before September 30, 2002. Fractures occurring within 14 days of a diagnosis code for an injury related to a motor vehicle accident were not included. The index date for cases was the date of their first non-vertebral fracture. Controls were selected from the eligible cohort of patients without a non-vertebral fracture. Controls were individually matched to cases (4:1) on date of COPD diagnosis, age, and sex and assigned the index date of their matched case.

Inhaled corticosteroid exposure was determined from prescriptions dispensed between COPD diagnosis date and index date. Doses were converted to beclomethasone equivalents (19) and cumulative exposure was calculated. The average daily dose was calculated for each patient and categorized into low (<300 μg per day), medium (300 μg – 699 μg per day), and high doses (≥700 μg per day) (11).

Additional covariates measured were factors associated with fractures and/or inhaled corticosteroid use. Exposure to both systemic and topical steroids was measured during the follow-up period. We determined if patients filled

prescriptions for the following medications: anticonvulsants, methotrexate, thiazide diuretics, anxiolytics, antipsychotics, antidepressants, anti-Parkinson medications, hormone replacement therapy, bisphosphonates, and vitamin D. Patients were classified with the following comorbidities if they had at least two visits with a diagnosis code for the condition: osteoporosis, osteopenia, diabetes, anemia, depression, dementia, psychoses, rheumatoid arthritis, Cushing's syndrome, hyperparathyroidism, inflammatory bowel disease, congestive heart failure, stroke, back pain, seizures, and a history of falls.

Conditional logistic regression was used to assess the association between inhaled corticosteroid exposure and the risk of non-vertebral fracture in patients with COPD (STATA, version 8) (20). Odds ratios (ORs) and 95% confidence intervals were used to quantify the risk of fractures in unadjusted and adjusted models. Adjusted models controlled for exposure to other medications (including oral corticosteroids), comorbidities and the number of hospitalizations. Separate ORs were estimated for any exposure during follow-up, recency of exposure, dose of exposure, and the interaction between recency of exposure and dose. Sensitivity analyses were conducted related to impact of oral corticosteroids, duration of follow-up time and dose category definitions.

The online data supplement is available for further details on methods.

Results

A total of 40,157 patients were included in the COPD cohort (Figure E1 in online data supplement). From the cohort, a total of 1708 cases were matched to 6817 controls. We were unable to match four controls to 9 cases and these cases have either 2 or 3 matched controls. The population was predominantly male (cases=94.4%, controls=94.6%) and the average age was 62.7 years (SD=12.4) in both cases and controls (Table 1). The average follow-up time was nearly 1.75 years (637 days in cases and 635 days in controls).

A total of 21.4% of cases were exposed to inhaled corticosteroids during the follow-up period, while 22.1% of controls were exposed (Table 2). Slightly more cases were exposed within 30 days (5.7% cases vs. 4.5% controls) and 90 days (11.3% cases vs. 9.7% controls) of their index date. When categorized by average daily dose (11), a higher proportion of cases were in the high dose category (6.3% vs. 5.2%). The average daily dose was 156.7 μg in the cases and 137.9 μg in the controls. Additionally, a higher proportion of cases were exposed to oral corticosteroids during the follow-up period (21.3% vs. 16.8%) and the average cumulative exposure was also higher in the cases (314 mg vs. 192 mg).

The case patients had more annual COPD hospitalizations over the follow-up period than the controls, while the COPD-related outpatient visits were similar between the groups (Table 3). A larger proportion of cases had more than one

COPD-related hospitalization annually than the controls (4.9% vs. 3.3%, p=0.002). The higher number of annual hospitalizations in the case group led to more COPD-related hospital days in the cases. However, the annual COPD-related outpatient utilization was similar between the two groups with 75.2% of the cases and 76.5% of the controls averaging less than one visit per year (p=0.24).

Exposure to inhaled corticosteroids during the follow-up period was not associated with an increased risk of fractures in the unadjusted analysis (OR=0.96; 95% CI, 0.84 to 1.09) (Table 4). Adjustment for potentially confounding variables did not impact the risk of fracture (OR=0.97; 95% CI, 0.84 to 1.11). When the recency of exposure was considered (current users) the risk of non-vertebral fractures was increased in exposed patients. In those exposed to inhaled corticosteroids within 30 days of their index date the OR was 1.29 (95% CI, 1.02 to 1.64) in the unadjusted analysis and decreased to 1.20 with a 95% CI that includes one (95% CI, 0.94 to 1.54) when controlling for potential confounders.

In addition to increases in risk associated with the recency of exposure, the risk of non-vertebral fractures was also related to the dose of inhaled corticosteroids. Patients receiving the highest average daily dose were at an increased fracture risk. The risk of fracture was not increased in patients in the two lowest dose categories (Table 4). However, those exposed to an average of 700 μg per day

or more had an increased risk of non-vertebral fractures (OR=1.20; 95% CI, 0.95 to 1.52).

Further analyses indicated an interaction between current use and average daily dose. Patients classified as current users with exposure to inhaled corticosteroids at high daily doses were at the highest risk for non-vertebral fractures (Figure 1). The risk of non-vertebral fracture in this group was high in both the unadjusted (OR=1.71; 95% CI, 1.14 to 2.56) and adjusted (OR=1.68; 95% CI, 1.10 to 2.57) analyses. In the highest dose category the average daily dose was 1616 μg per day (SD=917) in the cases and 1469 μg per day (SD=944) in the controls.

Several additional analyses were conducted to test the robustness of the primary findings. Details on the findings from these can be found in the online data supplement. The risk of fracture associated with current, high dose use of inhaled corticosteroids was consistent regardless of how oral corticosteroid use was categorized (Table E3 in online data supplement). The recency or cumulative dose of oral corticosteroid exposure did not modify the risk of fractures associated with inhaled corticosteroid exposure. Additionally, the risk of fractures was similar in these patients when the analysis was restricted to patients not exposed to oral corticosteroids during the follow-up period (Adjusted OR = 1.55).

An analysis was performed that was restricted to patients with at least two years of follow-up time. Patients with current and recent exposure had increased risks of fractures (Current User OR=1.48 [95% CI, 1.03 to 2.14]; Recent User OR=1.50 [95% CI, 1.15 to 1.96]) (Table E4 in online data supplement). The odds ratio in current users of high doses was 2.45 (95% CI, 1.42 to 4.22), while the odds ratios in the other categories were consistent with no marked increase in the risk of fractures. To test the impact of drug categorization, drug dosings were re-categorized according to NAEPP criteria. In this analysis the odds ratio in current users of high doses was 1.75 (95% CI, 1.09 to 2.82), while the odds ratios in the other categories were consistent with no increase in the risk of fractures.

Discussion

The objective of this study was to determine if inhaled corticosteroids are associated with an increased risk of fractures in patients with COPD. The results of the analysis indicate that when comparing patients ever exposed to inhaled corticosteroids during the follow-up period to those not exposed there is no increase in the risk of fractures associated with exposure. However, the risk of fractures does appear to be impacted by recent exposure and the average daily dose. Patients that were currently using inhaled corticosteroids at average doses greater than 700 μg beclomethasone equivalents per day had a slight increase in

the risk of fracture compared to COPD patients that never used inhaled corticosteroids.

The relation between an increased risk of fractures associated with recent use of high average daily doses observed in this analysis is consistent with findings in oral corticosteroid studies.(8, 21) An early increase in the risk of fractures was associated with patients using the highest daily doses of oral corticosteroids. However, a meta-analysis of the association between corticosteroid use and osteoporosis indicated cumulative dose had a stronger relation to decreased bone mineral density than did average daily dose.(22) As pointed out by van Staa et al., a potential explanation of these findings is that the association between corticosteroids and osteoporosis and fractures may be working through two mechanisms.(22) Changes in bone mineral density associated with chronic exposure to corticosteroids may be due to increased bone resorption at the cellular level, which is impacted by long-term exposure to corticosteroids.(22, 23) The mechanism associated with short-term impact of corticosteroids on fractures may result from increased osteocyte apoptosis.(24) Manolagas speculated that osteocyte apoptosis could lead to an increase in the risk of fracture due to a short-term reduction in bone quality.(24) Thus the impact of corticosteroids on fractures could be related to both the short-term effect of high doses on osteocyte apoptosis and the long-term decrease in bone mineral density due to increased bone resorption. The results of the analysis restricted to patients with at least two years of follow-up indicates that patients may be experiencing

decreased bone quality from both acute high dose exposure as well as long-term exposure.

Importantly, the evidence related to both acute as well as chronic effects of steroids is from studies of systemic corticosteroid exposure. However, studies of inhaled corticosteroids have shown there are dose-related systemic effects on bone density.(25-28) Inhaled corticosteroids have been shown to significantly decrease bone density in as little as a one-year period of exposure.(27) Also, with systemic corticosteroids there has been evidence of a decline in the risk of fracture upon cessation of therapy.(8) Therefore, the results of this study are consistent with the evidence of a systemic effect on bone density from inhaled corticosteroids, which is likely related to the dose of the inhaled corticosteroid. That is, there is more of a systemic effect the higher the dose and in patients at relatively high risk it may be enough to lead to a fracture. Additionally, the risk is highest in those patients actively treated with inhaled corticosteroids, which we defined as current users in this analysis, and the risk of fracture is attenuated and even returns to normal upon cessation of therapy. Therefore, our observation that an increase in the risk of fractures in current users of the highest doses of inhaled corticosteroids is likely due to the systemic effects of active treatment with inhaled corticosteroids.

The results from this analysis add to the evidence on the association between inhaled corticosteroid use and the risk of fractures.(10-13) The results are

consistent with the findings from the van Staa et al. cohort study in the GPRD that assessed the risk of non-vertebral fracture associated with inhaled corticosteroid use.(11) They observed a dose-response association between inhaled corticosteroid use and the risk of non-vertebral fractures. The risk of non-vertebral fracture in the high dose group in that study (>700 μg beclomethasone equivalents/day) was 1.28 (95% CI, 1.15 to 1.42), while the point estimate in the high dose group in this analysis was 1.20 (95% CI, 0.95 to 1.52). However, van Staa et al. do not present an evaluation of the risk in current versus past users of inhaled corticosteroids. Therefore, results from this analysis expand on the van Staa et al. findings by assessing the impact of current use.

Other observational studies of the risk of fracture associated with inhaled corticosteroid use have shown mixed results. Hubbard et al. in a case-control study using the GPRD found an increased risk of hip fracture associated with inhaled corticosteroid exposure (Adjusted OR=1.19; 95% CI, 1.10 to 1.28) in patients with asthma or COPD.(10) In a study of elderly women in Ontario, Canada, Lau et al. found no increase in the risk of hip fractures in those exposed to inhaled corticosteroids compared to those exposed to proton pump inhibitors (Adjusted RR=0.92; 95% CI, 0.75 to 1.12).(12) However, the average duration of follow-up in the inhaled corticosteroid group was less than 300 days. Finally, Suissa et al., in a case-control study of patients from Quebec, Canada, reported no increase in the risk of non-vertebral fractures associated with ever exposure (Adjusted OR=0.96; 95% CI, 0.91 to 1.01).(13) However, they report an

increased risk of fracture of 1.06 (95% CI, 1.01 to 1.12) with every 1000 μg increase in dose.(13) All but the Lau et al. paper examine the impact of current use and dose on fracture risk; however, none of the previous studies report the impact of the combination of dose and active use. Our analysis indicates that both factors play a role in understanding the risk of fractures associated with inhaled corticosteroid exposure.

Results from both this study and that of previous observational studies demonstrate a slight increase in the risk of non-vertebral fractures associated with high dose inhaled corticosteroid use. Van Staa et al. conclude the risk is more a result of the severity of disease rather than exposure to inhaled corticosteroids. To attempt to control for differences in severity, we restricted the cohort to patients with a new diagnosis of COPD that were treated during the follow-up time period. Additionally, the analysis was adjusted for the number of annual hospitalizations. Other measures were also assessed as proxies for disease severity. Neither the intensity of COPD-specific healthcare service utilization nor the number of classes of respiratory medications patients were taking impacted the estimated risk of fractures associated with ICS exposure. Factors which have been previously used as markers for disease severity in analyses of COPD patients.(29)

In addition to disease severity, comorbidities related to ICS use or fractures were included as covariates in the analysis. While the analysis accounts for the

individual comorbidities, the potential interaction between comorbidities was not included in the analysis. Because many of these patients have multiple chronic diseases it is possible that the combination of certain diseases puts patients at higher risks for fractures. That is, patients with certain combinations may be frailer than other patients and it is these individuals most impacted by the effect of inhaled corticosteroids. A measure of frailty may be an important covariate in future analyses assessing the risk of fractures associated with ICS use.

Our results indicate that in VA patients with COPD, the current use of high dose inhaled corticosteroids is associated with a slight increase in the risk of non-vertebral fractures. The increase in the risk of fracture associated with inhaled corticosteroid use found in this study does not by itself warrant the stopping of treatment in patients with COPD. However, evidence from this and other epidemiological studies (10, 11) of inhaled corticosteroid dose and the risk of fractures indicate providers should consider prescribing the lowest effective dose of inhaled corticosteroids in the management of COPD.

Acknowledgments

We would like to thank Brian Bartle and Jianglin Xu for their assistance with this project, Ramon A. Durazo-Arvizu for his statistical input and Kourtney J. Davis for her valuable comments.

References

1. Roche N, Lepage T, Bourcereau J, Terrioux P. Guidelines versus clinical practice in the treatment of chronic obstructive pulmonary disease. *Eur Respir J* 2001;18:903-908.

2. The pharmalogical management of chronic obstructive pulmonary disease. Washington, DC: Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel, Veterans Health Administration, Department of Veterans Affairs; September 2002. PBM-MAP Publication 02-0012.

3. Management of Chronic Obstructive Pulmonary Disease. Washington, DC: VA/DoD Clinical Practice Guideline Working Group, Veterans Health Administration, Department of Veterans Affairs and Health Affairs, Department of Defense, August 1999. Office of Quality and Performance publication 10Q-CPG/COPD-00.

4. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1995;152:S77-S120.

5. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 2001;163:1256-1276.

6. Siafakas NM, Vermeire P, Pride NB, Paoletti P, Gibson J, Howard P, Yernault JC, Decramer M, Higenbottam T, Postma DS et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. *Eur Respir J* 1995;8:1398-1420.

7. The COPD Guidelines Group of the Standards of Care Committee of the BTS. BTS guidelines for the management of chronic obstructive pulmonary disease. *Thorax* 1997;52 Suppl 5:S1-28.

8. van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. *J Bone Miner Res* 2000;15:993-1000.

9. Woodcock A. Effects of inhaled corticosteroids on bone density and metabolism. *J Allergy Clin Immunol* 1998;101:S456-S459.

10. Hubbard RB, Smith CJ, Smeeth L, Harrison TW, Tattersfield AE. Inhaled corticosteroids and hip fracture: a population-based case-control study. *Am J Respir Crit Care Med* 2002;166:1563-1566.

11. van Staa TP, Leufkens HG, Cooper C. Use of inhaled corticosteroids and risk of fractures. *J Bone Miner Res* 2001;16:581-588.

12. Lau E, Mamdani M, Tu K. Inhaled or systemic corticosteroids and the risk of hospitalization for hip fracture among elderly women. *Am J Med* 2003;114:142-145.

13. Suissa, S., M. Baltzan, R. Kremer, and P. Ernst. 2003. Inhaled Corticosteroid Use and the Risk of Fracture. *Am J Respir Crit Care Med* 2004; 169:83-88.

14. Biskobing DM. COPD and osteoporosis. *Chest* 2002;121:609-620.

15. Incalzi RA, Caradonna P, Ranieri P, Basso S, Fuso L, Pagano F, Ciappi G, Pistelli R. Correlates of osteoporosis in chronic obstructive pulmonary disease. *Respir Med* 2000;94:1079-1084.

16. Iqbal F, Michaelson J, Thaler L, Rubin J, Roman J, Nanes MS. Declining bone mass in men with chronic pulmonary disease: contribution of glucocorticoid treatment, body mass index, and gonadal function. *Chest* 1999;116:1616-1624.

17. Lee TA, Bartle B, Xu J, Davis KJ, Weiss KB. The association between inhaled corticosteroid use and fractures in veterans with chronic obstructive pulmonary disease [abstract]. *Chest* 2003;124:166S.

18. Lee TA, Bartle B, Xu J, Davis KJ, Weiss KB. The risk of fractures associated with inhaled corticosteroid use in patients with COPD [abstact]. *US COPD Coalition National Conference* 2003;1186.

19. Kelly HW. Comparison of inhaled corticosteroids. *Ann Pharmacother* 1998;32:220-232.

20. Hosmer DW, Lemeshow S. Applied logistic regression. New York: Wiley; 1989.

21. van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. *Rheumatology (Oxford)* 2000;39:1383-1389.

22. van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. *Osteoporos Int* 2002;13:777-787.

23. Weinstein RS, Jilka RL, Parfitt AM, Manolagas SC. Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids. Potential mechanisms of their deleterious effects on bone. *J Clin Invest* 1998;102:274-282.

24. Manolagas SC. Corticosteroids and fractures: a close encounter of the third cell kind. *J Bone Miner Res* 2000;15:1001-1005.

25. Hanania NA, Chapman KR, Sturtridge WC, Szalai JP, Kesten S. Dose-related decrease in bone density among asthmatic patients treated with inhaled corticosteroids. *J Allergy Clin Immunol* 1995;96:571-579.

26. Ip M, Lam K, Yam L, Kung A, Ng M. Decreased bone mineral density in premenopausal asthma patients receiving long-term inhaled steroids. *Chest* 1994;105:1722-1727.

27. Israel E, Banerjee TR, Fitzmaurice GM, Kotlov TV, LaHive K, LeBoff MS. Effects of inhaled glucocorticoids on bone density in premenopausal women. *N Engl J Med* 2001;345:941-947.

28. The Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med* 2000;343:1902-1909.

29. Fan VS, Bryson CL, Curtis JR, Fihn SD, Bridevaux P-O, McDonell MB, Au DH. Inhaled corticosteroids in chronic obstructive pulmonary disease and risk of death. *Am J Respir Crit Care Med* 2003; 168:1488-1494.

Figure Legends

Figure 1. Risk of non-vertebral fracture by recency of exposure (current user vs. past user) and the average daily dose of exposure adjusted for asthma, other coexisting illness, concomitant medications, history of seizures and falls, and number of annual hospitalizations

Tables

Table 1. Descriptive information on the cases and controls

	Cases N=1708		Controls N=6817	
Age, N (%)				
<50	287	(16.8)	1148	(16.8)
50-59	412	(24.1)	1648	(24.2)
60-69	433	(25.4)	1729	(25.4)
70-79	447	(26.2)	1778	(26.1)
≥80	129	(7.6)	514	(7.5)
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)
Covariates in adjusted models				
Comorbidities, N (%)				
Asthma	338	(19.8)	1303	(19.1)
Osteoporosis	85	(5.0)	187	(2.7)
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)
CHF	523	(30.6)	1836	(26.9)
History of Seizures	183	(10.7)	448	(6.6)
Stroke	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)
Number of Annual Hospitalizations, N (%)				
0	760	(44.5)	4496	(66.0)
>0 to <2	666	(39.0)	1806	(26.5)
≥ 2	282	(16.5)	515	(7.6)

Table 2. Oral and inhaled corticosteroid use in cases and controls

	Cases		Controls	
	N=1708		**N=6817**	
Oral Corticosteroid Exposure, N (%)				
Ever	364	(21.3)	1146	(16.8)
≤ 60 days prior to index date	86	(5.0)	216	(3.2)
Cumulative Dose*, Mean (SD)	314.1 mg	(1746)	191.9 mg	(994)
ICS Exposure, N (%)				
Ever	365	(21.4)	1508	(22.1)
≤ 30 days prior to index date	98	(5.7)	307	(4.5)
≤ 90 days prior to index date	193	(11.3)	664	(9.7)
Avg. Daily Dose†, Mean (SD)	156.7 μg	(467.2)	137.9 μg	(409.1)
Cumulative Dose†, Mean (SD)	42,950 μg	(160,431)	39,276 μg	(156440)
Avg. Daily Dose†, N (%)				
< 300 μg	108	(6.3)	526	(7.7)
300 – 699 μg	149	(8.7)	626	(9.2)
≥ 700 μg	108	(6.3)	356	(5.2)

* Doses in prednisone equivalents
† Doses in beclomethasone equivalents

Table 3. Annual COPD-related healthcare utilization during the follow-up period

	Cases		Controls		p-values
	N=1708		N=6817		
Annual COPD hospitalizations, N (%)					
<1	1625	(95.1)	6591	(96.7)	0.002
≥1	83	(4.9)	226	(3.3)	
Number of days in hospital annually for COPD, N (%)					
0	1625	(95.1)	6591	(96.7)	0.009
>0 to <7	68	(4.0)	188	(2.8)	
≥7	15	(0.9)	38	(0.6)	
Annual number of outpatient visits for COPD, N (%)					
<1	1284	(75.2)	5218	(76.5)	0.24
≥ 1 to < 3	332	(19.4)	1293	(19.0)	
≥3	92	(5.4)	306	(4.5)	

Table 4. Risk of non-vertebral fracture by categories of exposure to inhaled corticosteroids (ICS)

	Cases		Controls		Unadjusted OR [95% CI]		Adjusted OR* [95% CI]	
No ICS During Follow-up	1343	(78.6)	5309	(77.9)	1.00	–	1.00	–
ICS During Follow-up	365	(21.4)	1508	(22.1)	0.96	[0.84 to 1.09]	0.97	[0.84 to 1.11]
Non-current user	1610	(94.3)	6510	(95.5)	1.00	–	1.00	–
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]
Non-recent user	1515	(98.7)	6153	(90.3)	1.00	–	1.00	–
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								
No ICS	1343	(78.6)	5309	(77.9)	1.00	–	1.00	–
< 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]

* Adjusted for comorbidities, medications and annual hospitalizations listed in Table 1 and oral corticosteroid use

Figures

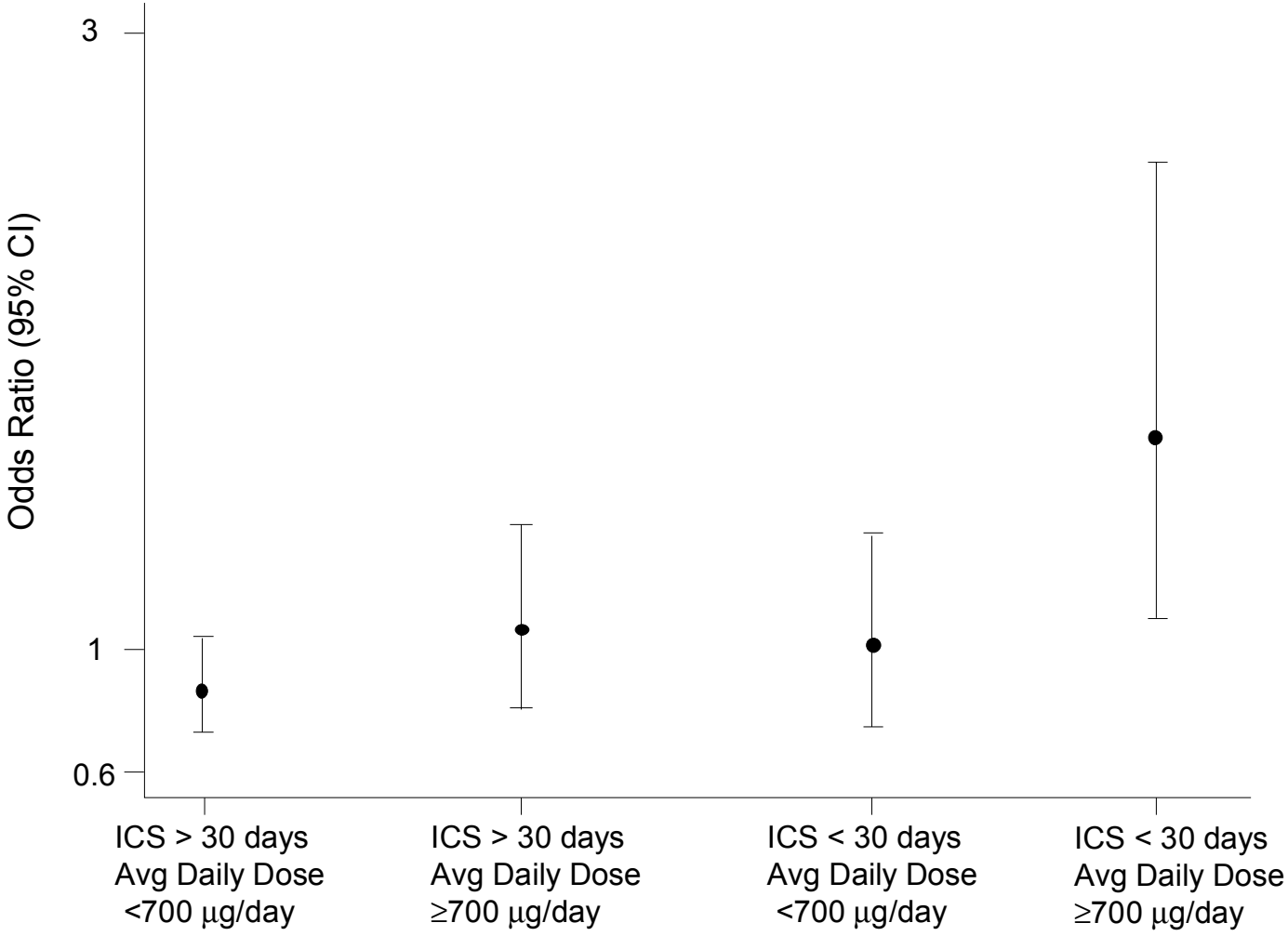

3
1
0.6
Odds Ratio (95% CI)
ICS > 30 days
Avg Daily Dose
<700 µg/day
ICS > 30 days
Avg Daily Dose
≥700 µg/day
ICS < 30 days
Avg Daily Dose
<700 µg/day
ICS < 30 days
Avg Daily Dose
≥700 µg/day
ICS Exposure

Figure 1

Fracture Risk Associated with Inhaled Corticosteroid Use in Chronic Obstructive Pulmonary Disease

Todd A. Lee[a,b,c], Kevin B. Weiss[a,b]

Online Data Supplement

The following section contains a detailed description of the methods used to evaluate the risk of non-vertebral fractures associated with inhaled corticosteroid use in patients with chronic obstructive pulmonary disease (COPD).

General Overview

We conducted a nested case-control study of Veterans Affairs (VA) patients with a new diagnosis of COPD between October 1, 1998 and September 30, 1999 and receiving COPD-related medication during the follow-up period. Cases were identified based on a diagnosis of non-vertebral fracture, between January 1999 and September 2002. Cases were individually matched to controls. Inhaled corticosteroid exposure was quantified as beclomethasone equivalents and based on pharmacy dispensing data. The association between inhaled corticosteroid use and non-vertebral fractures was quantified using conditional logistic regression models.

Study Databases

To conduct the study we used data from the VA inpatient, outpatient, pharmacy and beneficiary databases. The inpatient and outpatient database contain information on all medical encounters within the VA system. All inpatient visits are coded with a primary diagnosis code (ICD-9) and can include up to 9 additional diagnoses. Procedures conducted during an inpatient stay are coded with ICD-9 procedure codes. The outpatient visit data also contains information on diagnoses (ICD-9 codes) that includes a primary diagnosis as well as up to 9

secondary diagnoses. Procedures conducted in the outpatient setting are identified using CPT procedure codes.

Outpatient medication use is available in a database maintained by the Pharmacy Benefit Management group. The data contains records for outpatient medications dispensed to VA patients and includes information such as the medication, dose, dosing instructions and days supply. The pharmacy data is available beginning October 1, 1998 and can be linked to the inpatient and outpatient data. Finally, a beneficiary database was used to identify patients that died during the follow-up period and their date of death.

The VA databases were used to identify a cohort of patients with COPD, and subsequently identify non-vertebral fractures within the cohort and determine exposure to inhaled corticosteroids.

Cohort Definition

Patients with COPD were identified using data between October 1, 1997 and September 30, 1999. Patients with incident treatment of COPD in the VA were identified. That is, patients were receiving care in the VA prior to their COPD diagnosis, but did not have a history of COPD diagnoses. To ensure total exposure to inhaled corticosteroids within the VA system was captured, patients were excluded if they filled a prescription for a respiratory medication within 90

days of October 1, 1998 (Table E1). Specifically, to be included in the cohort patients must have met the following inclusion criteria:

- **any** ICD-9 code (491.x, 492.x, 496) for COPD at an inpatient or outpatient encounter between October 1, 1998 and September 30, 1999;
- **no** ICD-9 code for COPD at an inpatient or outpatient encounter between October 1, 1997 and September 30, 1998;
- at least **one** VA inpatient or outpatient visit between October 1, 1997 and September 30, 1998;
- **no** prescription for a respiratory medication in the 90 days following October 1, 1998;
- **no** fracture in the 90 days following October 1, 1998; and
- filled at least **one** prescription for a respiratory medication (Table E1) during the follow-up period.

The number of patients meeting each of the inclusion criteria is shown in Figure E1.

Case Selection

Cases were patients from the study cohort with non-vertebral fractures occurring after their initial COPD diagnosis date from January 1, 1999 through September 30, 2002. Non-vertebral fractures were identified with diagnostic and procedure codes (Table E2). Fractures occurring within 14 days of a diagnosis code for an injury related to a motor vehicle accident were not included. Fractures were

identified as hip, wrist or other non-vertebral fractures. The index date for each case was the date of their first non-vertebral fracture.

Control Selection

Controls were selected from the eligible cohort of patients without 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 by quarter (Quarter 1, Quarter 2, Quarter 3, Quarter 4), age at COPD diagnosis (<40, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85-89, ≥90) and sex. Controls were randomly drawn from the pool of potential controls until each case had 4 matched controls. Controls were assigned the index date of their matched cases.

Inhaled Corticosteroid Exposure

All inhaled corticosteroid prescriptions dispensed between the COPD diagnosis date and the index date were identified for cases and controls. Information from the dosing instructions was used to determine the total number of doses per day and used to calculate the days supply based on the number of actuations per container. Doses of inhaled corticosteroids were converted to beclomethasone equivalents (E1) and cumulative exposure was calculated. Additionally, the average daily dose of inhaled corticosteroids 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).(E2)

Exposure was classified as ever/never during the follow-up period, in addition to recent use (≤30 days, ≤90 days) to identify current users versus those that had discontinued use. Patients with a supply of ICS within 30 days of their index date were classified as current users while those with a supply within 90 days of their index date were classified as recent users.

Covariates

Additional covariates were measured using pharmacy, inpatient and outpatient data. We measured exposure to both systemic and topical corticosteroids. Oral corticosteroid use was documented as cumulative dose during follow-up time, presence of a recent steroid prescription (≤60 days prior to index date), and any exposure during the follow-up period. Oral corticosteroid doses were converted to prednisone equivalent units. In addition, we documented exposure to other non-systemic corticosteroids, including nasal and topical formulations. Use was classified as ever/never users of other non-systemic corticosteroids.

Other covariates measured included factors known to be associated with fractures and/or inhaled corticosteroids use. We determined if patients had been exposed to any of the following medications which affect bone density or risk of falls: 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. The medical conditions were osteoporosis, osteopenia, diabetes, anemia, depression, dementia, psychoses, rheumatoid arthritis, Cushing's syndrome, hyperparathyroidism, inflammatory bowel disease, congestive heart failure, stroke, back pain, seizures, and a history of falls.

We considered healthcare utilization as a measure of overall health status and disease severity. We categorized the annual number of hospitalizations per patient into 0, >0 to <2 and ≥ 2. We also identified COPD-related healthcare utilization using ICD-9 codes for individual healthcare encounters. The annual number of COPD-related hospitalizations and outpatient visits was calculated for each patient.

Analysis

All analyses were conducted using STATA version 8 statistical software. We used conditional logistic regression to assess the effect of exposure to inhaled corticosteroids on the risk of fracture in patients with COPD. Odds ratios (ORs) and 95% confidence intervals were used to quantify the risk of fractures in unadjusted and adjusted models. The unadjusted effect of inhaled corticosteroids on the risk of non-vertebral fracture was assessed with conditional logistic regression models where the exposure variable was the only predictor

included in the model. In adjusted analyses, we controlled for medication exposure, medical conditions, and number of hospitalizations. Separate models were fit to examine the risk in various exposure categories. Models were fit to evaluate the risk of any exposure during the follow-up period, the risk of current exposure, the risk of recent exposure, the risk by dose of exposure, and the interaction between recency of exposure and dose.

We conducted sensitivity analyses related to the duration of follow-up time and the definitions of the inhaled corticosteroid doses. To determine if exposure to oral corticosteroids modified the results, we examined the impact of recent oral steroid exposure, cumulative steroid exposure and a combination of recency of exposure and dose. To determine if follow-up time affected the results, an analysis that included only patients with follow-up time of 2 years or more was conducted. To determine if alternative categorizations of low, medium and high doses impacted the results, we categorized dose according to the NAEPP criteria of low (<504 μg/day), medium (504-840 μg/day) and high (>840 μg/day) doses of beclomethasone.(E3)

References

E1. Kelly HW. Comparison of inhaled corticosteroids. *Ann Pharmacother* 1998;32:220-232.

E2. van Staa TP, Leufkens HG, Cooper C. Use of inhaled corticosteroids and risk of fractures. *J Bone Miner Res* 2001;16:581-588.

E3. National Institutes of Health, National Heart, Lung and Blood Institute. Guidelines for the diagnosis and management of asthma: Expert panel report 2. Bethesda, MD: U.S. Government Printing Office; 1997. NIH Publication No. 97-4051.

Figure Legends

Figure E1. Number of patients meeting each criterion for inclusion in the study cohort

Tables

Table E1. Classes of medications defined as respiratory-related medications used to treat COPD

Medication class	**Specific medications**
Short-acting β_2-agonists	Albuterol, metaproterenol, terbutaline
Long-acting β_2-agonists	Salmeterol
Anticholinergics	Ipratropium
Methylxanthines	Theophylline
Inhaled corticosteroids	Beclamethasone, flunisolide, fluticasone, triamcinolone
Combination products	Advair®, Combivent®

Table E2. Diagnostic and procedure codes for case identification and classification of events

Event	**ICD-9 Diagnosis Codes**	**ICD-9 Procedure Codes**	**CPT Codes**
Hip Fracture	733.14, 820.xx		27193 – 27248, 27254
Wrist Fracture	733.12, 813.xx	79.0, 79.1, 79.2, 79.3 (4^{th} digit = 2)	25500 – 25605, 25611 – 25650, 25680, 25685
Other Non-vertebral Fracture	733.10, 733.11, 733.15, 733.16, 733.19, 810.xx – 812.xx, 814.xx – 819.xx, 821.xx – 829.xx	79.0, 79.1, 79.2, 79.3 (4^{th} digit = 0, 1, 3, 4, 5, 6, 7, 8, 9)	24500 – 24587, 27500 – 27514, 27520 – 27540, 27750 – 27828, 24620, 24635, 24650 – 24685

Table E3. Risk of non-vertebral fractures associated with inhaled corticosteroid exposure using various categories of oral corticosteroid exposure

	Adjusted OR* [95% CI]	
Ever used oral corticosteroids		
Never used ICS	1.00	–
Past user (>30 days), Avg. Daily Dose <700 μg/day	0.87	[0.72 to 1.03]
Past user (>30 days), Avg. Daily Dose ≥700 μg/day	1.06	[0.80 to 1.40]
Current user (≤30 days), Avg. Daily Dose <700 μg/day	1.01	[0.75 to 1.37]
Current user (≤30 days), Avg. Daily Dose ≥700 μg/day	1.68	[1.10 to 2.58]
Recent oral corticosteroid use (< 30 days before index date)		
Never used ICS	1.00	–
Past user (>30 days), Avg. Daily Dose <700 μg/day	0.87	[0.73 to 1.04]
Past user (>30 days), Avg. Daily Dose ≥700 μg/day	1.07	[0.81 to 1.41]
Current user (≤30 days), Avg. Daily Dose <700 μg/day	1.00	[0.74 to 1.36]
Current user (≤30 days), Avg. Daily Dose ≥700 μg/day	1.67	[1.09 to 2.55]
Cumulative oral corticosteroid exposure†		
Never used ICS	1.00	–
Past user (>30 days), Avg. Daily Dose <700 μg/day	0.86	[0.72 to 1.03]
Past user (>30 days), Avg. Daily Dose ≥700 μg/day	1.06	[0.80 to 1.40]
Current user (≤30 days), Avg. Daily Dose <700 μg/day	1.01	[0.74 to 1.36]
Current user (≤30 days), Avg. Daily Dose ≥700 μg/day	1.68	[1.10 to 2.57]

* Adjusted for comorbidities, medications and annual hospitalizations listed in Table 1 and oral corticosteroid use as defined in the table

† Cumulative exposure divided into three categories: 1) No exposure; 2) 1 – 500 mg and 3) > 500 mg

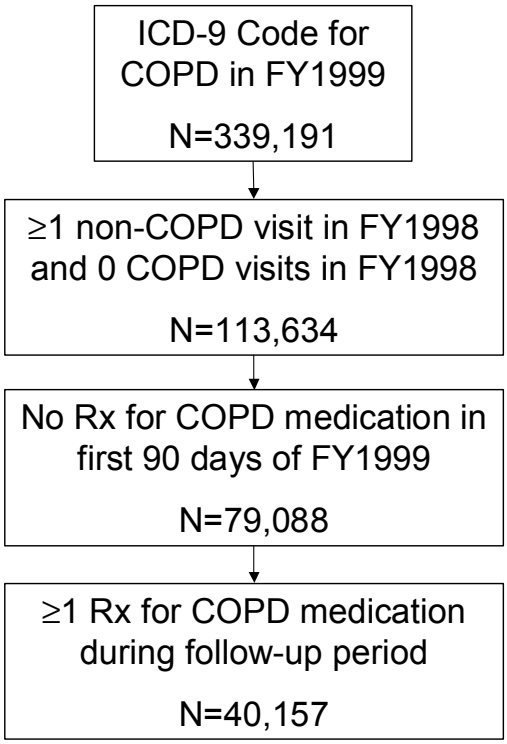
Table E4. Risk of non-vertebral fractures by categories of exposure in patients with at least two years of follow-up*

	Unadjusted OR [95% CI]		Adjusted OR† [95% CI]	
No ICS‡ in Follow-up Period	1.00	–	1.00	–
ICS‡ Ever in Follow-up Period	0.99	[0.82 to 1.20]	1.03	[0.84 to 1.27]
No ICS‡ use in last 30 days	1.00	–	1.00	–
Current user (ICS‡ in last 30 days)	1.49	[1.05 to 2.10]	1.48	[1.03 to 2.14]
No ICS‡ use in last 90 days	1.00	–	1.00	–
Recent user (ICS‡ in last 90 days)	1.54	[1.21 to 1.97]	1.50	[1.15 to 1.96]
Average Daily Dose				
Never user	1.00	–	1.00	–
< 300 μg	0.74	[0.54 to 1.02]	0.78	[0.56 to 1.10]
300 – 699 μg	0.96	[0.73 to 1.26]	1.02	[0.76 to 1.37]
≥ 700 μg	1.38	[1.03 to 1.85]	1.37	[1.00 to 1.88]
Recency & Dose of Exposure				
Never user	1.00	–	1.00	–
Past user (>30 days), Avg. Daily Dose <700 μg/day	0.84	[0.66 to 1.06]	0.89	[0.70 to 1.15]
Past user (>30 days), Avg. Daily Dose ≥700 μg/day	1.11	[0.78 to 1.57]	1.10	[0.75 to 1.59]
Current user (≤30 days), Avg. Daily Dose <700 μg/day	0.98	[0.61 to 1.58]	0.99	[0.60 to 1.65]
Current user (≤30 days), Avg. Daily Dose ≥700 μg/day	2.46	[1.48 to 4.08]	2.45	[1.42 to 4.22]

* Data set restricted to patients with at least 730 days of follow-up
† Adjusted for comorbidities, medications and annual hospitalizations (see Table 1 for complete list)
‡ ICS = Inhaled corticosteroids

Figures

Figure E1


ICD-9 Code for COPD in FY1999
N=339,191
≥1 non-COPD visit in FY1998 and 0 COPD visits in FY1998
N=113,634
No Rx for COPD medication in first 90 days of FY1999
N=79,088
≥1 Rx for COPD medication during follow-up period
N=40,157