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ORIGINAL RESEARCH

Chronic Obstructive Pulmonary Disease and Incidence of Hip Fracture: A Nested Case–Control Study in the EpiChron Cohort

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Purpose: To determine whether chronic obstructive pulmonary disease (COPD) is a risk factor for hip fracture and identify other factors associated with hip fracture.

Patients and Methods: Observational nested case–control study was conducted in Aragon, Spain in 2010. We included COPD patients aged >40 years, in the EpiChron cohort. Each COPD patient was matched for age, sex, and number of comorbidities with a control subject without COPD. Patients with an existing diagnosis of osteoporosis and those with hip fracture before 2011 were excluded. We collected baseline demographic, comorbidity, and pharmacological treatment data. During a 5-year follow-up period, we recorded the incidence of hip fracture. A logistic regression model was constructed to identify factors associated with hip fracture.

Results: The study population consisted of 26,517 COPD patients and the same number of controls (median [interquartile range] age, 74 [17] years; women, 24.7%). Smoking and heart failure were more frequent in COPD patients, and obesity, hypertension, diabetes, dyslipidemia, stroke, arthritis, and visual or hearing impairment were less frequent (all p<0.001). Consumption of benzodiazepines (p=0.037), bronchodilators (p<0.001), and corticosteroids (p<0.001) was higher in the COPD group, while that of beta-blockers and thiazides was lower (both p<0.001). During follow-up, 898 (1.7%) patients experienced hip fracture, with no differences observed between COPD and control patients. Multivariate analysis revealed that independent of COPD status, age, female sex, chronic liver disease, heart failure, and benzodiazepine use were independently associated with a higher risk of hip fracture, and obesity with a lower risk. In COPD patients, use of inhaled anticholinergics was independently associated with hip fracture (OR, 1.390; 95% CI 1.134–1.702; p=0.001).

Conclusion: COPD is not a risk factor for a hip fracture within 5 years. The association between the use of inhaled anticholinergics and risk of hip fracture warrants further study.

Keywords: chronic obstructive pulmonary disease, hip fracture, case–control study, incidence

Introduction

The world population is aging. Recent years have seen an increase in life expectancy in Spain and in the rest of the world. According to the World Health Organization, between 2015 and 2050 the proportion of the population aged 60 years and over will increase from 12% to 22% worldwide, an increase of 1.1 billion.[1]

Hip fracture is an age-associated health problem that frequently causes disability and worsening quality of life, leading to high healthcare costs and high mortality.[2] Frailty and osteoporosis are known causes of hip fracture.[3]

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Chronic obstructive pulmonary disease (COPD) constitutes a public health problem owing to its high prevalence, morbidity, and mortality. The World Health Organization estimates that by 2030 COPD will become the third cause of death globally.[4] In addition to affecting the airways, COPD also has extrapulmonary effects. Malnutrition, falls, and osteoporosis, all of which are also associated with hip fracture, are more frequent in COPD patients.[5–7]

Some studies have reported a decrease in bone mass in COPD patients.[8] Using the FRAX tool, a study of COPD patients hospitalized for exacerbation found that half of all patients were at high risk of hip fracture within 10 years.[9]

The objective of this study was to determine the incidence of hip fracture in COPD patients and to identify possible factors related to its occurrence.

Patients and Methods

Design

We conducted an observational nested case–control study in the EpiChron cohort in 2010. The cohort, which has been previously described,[10] consisted of anonymous demographic, clinical, and drug dispensing data from all users of the public health system of Aragon, Spain. The Spanish national health system provides free healthcare with universal coverage to approximately 95% of the population in Aragon.

Participants

We included the individuals >40 years old in the EpiChron cohort with a diagnosis of COPD recorded in their primary healthcare and/or hospital electronic records. Patients with a previous diagnosis of osteoporosis and those who had experienced hip fracture before 2010 were excluded. For each case, we selected a COPD-free control matched for age, sex, and number of comorbidities.

For each patient, the following variables were collected: age, sex, smoking status, alcohol consumption, diagnosed chronic diseases, and prescribed drugs. Disease diagnoses recorded in primary care and hospital electronic health records were coded according to the International Classification of Primary Care (ICPC) and the International Classification of Diseases, 9th Revision (ICD-9), respectively. Prescribed drugs were classified according to the third level of the Anatomical Therapeutic Chemical (ATC) Classification System (ie, by pharmacological subgroup).

Participants were followed for 5 years (until December 31, 2015), or until death or removal from the database of health system users. The incidence of hip fracture, as defined by ICD-9 codes 820.0–820.9,[11] was recorded during the follow-up period.

The study was approved by the Clinical Research Ethics Committee of Aragón (PI 18/131) and carried out in accordance with the principles of the Declaration of Helsinki and Spain's Organic Law for the Protection of Personal Data. The ethics committee waived the requirement for informed consent given the epidemiological nature of the project, which used anonymized data and did not involve any type of intervention.

Statistical Analysis

We described the baseline demographic and clinical characteristics of the study population based on the presence or absence of COPD. Qualitative variables were expressed as frequencies or percentages and quantitative variables as the median and interquartile range. Qualitative variables were compared using the Chi-squared test and quantitative variables using the Mann Whitney *U*-test.

To study the factors associated with the incidence of hip fracture, we performed a logistic regression model with the enter method, using in the multivariate model those variables associated with p-value <0.1 in the univariate model. We constructed Kaplan–Meier curves to analyze the incidence of hip fracture and compared them using the Log rank test.

In every case, we established the level of statistical significance for a value of $p<0.05$. We used the Statistical Package for the Social Sciences (SPSS; version 21.0 for Windows) for all statistical analyses.

Results

Figure 1 shows the flowchart of included patients. In December 2010, the EpiChron cohort consisted of 1,314,450 subjects and 577,934 had no exclusion criteria. Of them, 26,517 had a diagnosis of COPD.

Patient Characteristics

The baseline characteristics of subjects with and without COPD are presented in Table 1. The median [interquartile range] age was 74 [17] years, and 24.7% of the study population were women. The prevalence of smoking and heart failure was higher in the COPD group (20.4% vs 11.8%, $p<0.001$, and 18.3% vs 13.0%, $p<0.001$, respectively), while that of obesity (18.3% vs 21.1%), high blood pressure (61.4% vs 70.4%), diabetes (27.0% vs 33.9%), dyslipidemia (43.8% vs 54.2%), stroke (14.5% vs 18.0%), arthritis (25.8% vs 32.8%),

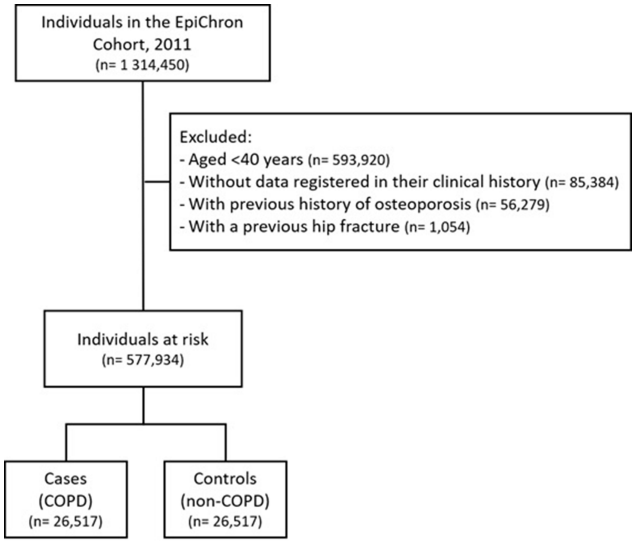

Figure 1 Flowchart of patients included in the study.

and visual (8.6% vs 10.0%) or hearing impairment (13.0% vs 15.5%) was lower (all p<0.001). Consumption of benzodiazepines (23.2% vs 22.4%; p=0.037), bronchodilators, and corticosteroids (both p<0.001) was higher in the COPD group, while that of beta-blockers and thiazides was lower (both p<0.001).

Incidence of Hip Fracture

During the 5-year follow-up period, 898 (1.7%) patients experienced hip fracture, with no evident differences in incidence between the COPD and the control group (Figure 2). Table 2 shows the differences between patients with and without hip fracture in COPD and control groups. There was no association between COPD and hip fracture (OR 1.042, 95% CI 0.913–1.189) even when we adjusted the model for age, sex, systemic corticosteroids, obesity, hypertension, hyperlipidemia, arthritis, heart failure, stroke, chronic liver disease, smoking, alcoholism, use of benzodiazepines, inhaled anticholinergics agents and calcium (OR 0.975, 95% CI 0.843–1.128). Multivariate analysis revealed that independent of COPD status, age, female sex, chronic liver disease, heart failure, and benzodiazepine use were independently associated with a higher risk of hip fracture, and obesity with a lower risk. Hyperlipidemia and stroke were associated with hip fracture in patients without COPD. The use of inhaled anticholinergics was independently associated with hip fracture in COPD patients (OR, 1.390; 95% CI 1.134–1.702; p = 0.001) (Table 3).

Table 1 Baseline Characteristics of the Study Population with and without Chronic Obstructive Pulmonary Disease (COPD)

Characteristics	With COPD (N= 26,517)	Without COPD (N= 26,517)	P value
Demographic and lifestyle (n, %)			
Women	6551 (24.7)	6551 (24.7)	1.000
Age (Median, IQR)	74 (17)	74 (17)	1.000
Body mass index (Median, IQR)	29.0 (6.4)	29.2 (5.8)	<0.001
Active smoking	5399 (20.4)	3131 (11.8)	<0.001
Alcoholism	5883 (22.2)	6026 (22.7)	0.139
Comorbidities (n, %)			
Number (Median, IQR)	4 (5)	5 (5)	<0.001
Obesity	4854 (18.3)	5577 (21.1)	<0.001
Hypertension	16,264 (61.4)	18,648 (70.4)	<0.001
Diabetes	7161 (27.0)	8972 (33.9)	<0.001
Hyperlipidemia	11,603 (43.8)	14,358 (54.2)	<0.001
Chronic liver disease	579 (2.2)	555 (2.1)	0.488
Heart failure	4849 (18.3)	3432 (13.0)	<0.001
Stroke	3831 (14.5)	4763 (18.0)	<0.001
Arthritis	6823 (25.8)	8676 (32.8)	<0.001
Visual impairment	2278 (8.6)	2645 (10.0)	<0.001
Hearing impairment	3437 (13.0)	4100 (15.5)	<0.001
Prescribed drugs (n, %)			
Benzodiazepines	6151 (23.2)	5948 (22.4)	0.037
Systemic corticosteroids	2044 (7.7)	1075 (4.1)	<0.001
Inhaled beta adrenergics, plain	3676 (13.9)	450 (1.7)	<0.001
Inhaled beta adrenergics, double therapy	7363 (27.8)	991 (3.7)	<0.001
Inhaled glucocorticoids	972 (3.7)	143 (0.5)	<0.001
Inhaled anticholinergics	7589 (28.6)	788 (3.0)	<0.001
Inhaled antiallergic agents	1 (0.0)	0 (0.0)	1.000
Systemic adrenergics, plain	22 (0.1)	8 (0.0)	0.018
Beta-blockers	2927 (11.0)	4744 (17.9)	<0.001
Thiazides	234 (0.9)	316 (1.2)	<0.001
Nonsteroidal anti-inflammatory drugs	3254 (12.3)	3351 (12.6)	0.207
Androgens	15 (0.1)	31 (0.1)	0.027
Estrogens	6 (0.0)	14 (0.1)	0.117
Calcium	637 (2.4)	632 (2.4)	0.910
Vitamin D	301 (1.1)	321 (1.2)	0.443
Bisphosphonates	288 (1.1)	250 (0.9)	0.109

Discussion

COPD is a poor prognostic factor in patients with hip fracture. Studies using databases in Japan, Denmark, the United Kingdom, and the United States have found that COPD is associated with higher mortality in the short and medium term in patients with hip fracture.[12–16] Moreover, COPD patients more frequently develop surgical wound

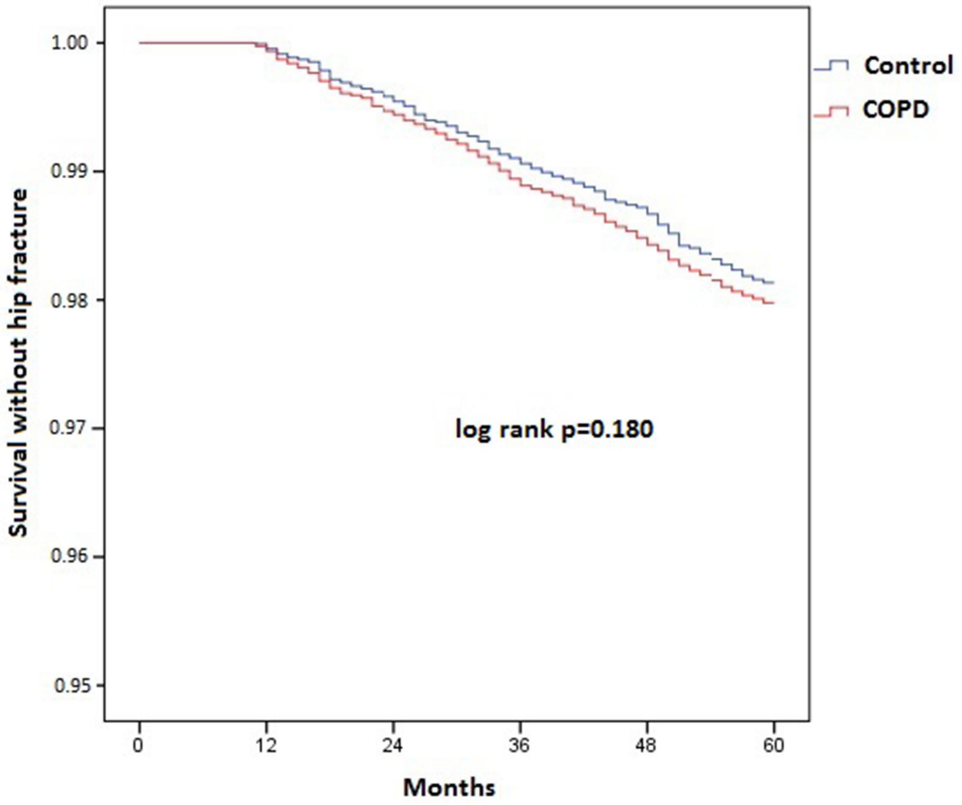

Figure 2 Kaplan–Meier curves of incidence of hip fracture.

infections, respiratory infections, and sepsis, have longer hospital stays and require more time for rehabilitation.[15–17]

Osteoporosis is an important comorbidity of COPD. It is frequently undiagnosed and is associated with poorer health and a poor prognosis.[18,19] Patients with both COPD and osteoporosis have more exacerbations and more hospitalizations.[20] Furthermore, a higher rate of COPD exacerbations has been associated with an increased risk of osteoporosis and a greater decrease in bone mass.[21,22] A cross-sectional study conducted in Spain measured the risk of hip fracture within the following ten years using the FRAX tool, and observed that half of all patients hospitalized for COPD had a high risk (>3%).[9] In a UK study, 40% of COPD patients in primary care were deemed high-risk based on FRAX score, and 45.6% based on the QFracture score.[23] Another UK study using the FRAX tool reported a high risk of hip fracture in outpatients with severe COPD.[24] In line with these findings, a recent study identified COPD as a risk factor for hip fracture.[25]

A retrospective observational study by Miguel et al selected patients hospitalized for hip fracture using the Spanish Minimum Basic Data Set and found that the incidence of hip fracture was higher in patients with COPD.[26] However, in this study, the incidence rates were calculated indirectly extrapolating data from other studies. Another Spanish population cohort study reported that of the comorbidities included in the Charlson index, COPD was associated with the occurrence of hip fracture in men with a relative risk of 1.20 (95% CI 1.03–1.40).[27] A retrospective case–control study of Taiwanese COPD patients found that the hazard ratio for hip fracture within two years was 1.57.[28] In the Norwegian Hordaland Health Study, in which the general population was followed for ten years, COPD was associated with a higher incidence of hip fracture,[8] and a greater degree of airway obstruction was associated with increased risk of hip fracture.

In contrast to previous studies, we did not observe an excess risk of hip fracture among COPD patients. Using an approach similar to ours, Akyea et al analyzed electronic health records and observed an increased risk of hip fracture among COPD patients, although this increase was not observed after adjusting for age, sex, Charlson index, body mass index, and the use of inhaled corticosteroids.[23] In our study, we matched patients by age, sex, and number of comorbidities. In the Hordaland Health Study, patients with COPD were significantly

Table 2 Characteristics of COPD Patients and Controls with and without Hip Fracture

Characteristics	COPD Patients			Controls		
	With HF (n=458)	Without HF (n=26,059)	P value	With HF (n=440)	Without HF (n=26,077)	P value
Demographic and lifestyle (n, %)						
Women	183 (40.0)	6368 (24.4)	<0.001	165 (37.5)	6386 (24.5)	<0.001
Age (Median, IQR)	83 (10)	74 (17)	<0.001	83 (10)	74 (17)	<0.001
Body mass index (Median, IQR)	27.5 (5.7)	29.0 (6.4)	<0.001	27.2 (5.7)	29.2 (5.8)	<0.001
Active smoking	42 (9.2)	5357 (20.6)	<0.001	18 (4.1)	3113 (11.9)	<0.001
Alcoholism	47 (10.3)	5836 (22.4)	<0.001	49 (11.1)	5977 (22.9)	<0.001
Comorbidities (n, %)						
Number (Median, IQR)	5 (5)	4 (5)	<0.001	7 (5)	5 (5)	<0.001
Obesity	59 (12.9)	4795 (18.4)	0.003	51 (11.6)	5526 (21.2)	<0.001
Hypertension	350 (76.4)	15,914 (61.1)	<0.001	358 (81.4)	18,290 (70.2)	<0.001
Diabetes	138 (30.1)	7023 (27.0)	0.147	170 (38.6)	8802 (33.8)	0.038
Hyperlipidemia	163 (35.6)	11,440 (44.0)	<0.001	184 (41.8)	14,174 (54.4)	<0.001
Chronic liver disease	17 (3.7)	562 (2.2)	0.037	17 (3.9)	538 (2.1)	0.015
Heart failure	169 (36.9)	4680 (18.0)	<0.001	121 (27.5)	3311 (12.7)	<0.001
Stroke	108 (23.6)	3723 (14.3)	<0.001	157 (35.7)	4606 (17.7)	<0.001
Arthritis	145 (31.7)	6678 (25.7)	0.004	167 (38.0)	8509 (32.7)	0.022
Visual impairment	46 (10.0)	2232 (8.6)	0.305	39 (8.9)	2606 (10.0)	0.477
Hearing impairment	73 (15.9)	3364 (12.9)	0.067	70 (15.9)	4030 (15.5)	0.853
Prescribed drugs (n, %)						
Benzodiazepines	151 (33.0)	6000 (23.0)	<0.001	132 (30.0)	5816 (22.3)	<0.001
Systemic corticosteroids	40 (8.7)	2004 (7.7)	0.458	15 (3.4)	1060 (4.1)	0.569
Inhaled beta adrenergics, plain	65 (14.2)	3611 (13.9)	0.891	9 (2.0)	441 (1.7)	0.701
Inhaled beta adrenergics, double therapy	132 (28.8)	7231 (27.7)	0.649	20 (4.5)	971 (3.7)	0.439
Inhaled glucocorticoids	20 (4.4)	952 (3.7)	0.496	2 (0.5)	141 (0.5)	1.000
Inhaled anticholinergics	156 (34.1)	7433 (28.1)	0.011	13 (3.0)	775 (3.0)	1.000
Inhaled antiallergic agents	0 (0.0)	1 (0.0)	1.000	0 (0.0)	0 (0.0)	1.000
Systemic adrenergics, plain	0 (0.0)	22 (0.1)	1.000	1 (0.2)	7 (0.0)	0.125
Beta-blockers	44 (9.6)	2883 (11.1)	0.362	86 (19.5)	4658 (17.9)	0.395
Thiazides	5 (1.1)	229 (0.9)	0.817	2 (0.5)	314 (1.2)	0.224
Nonsteroidal anti-inflammatory drugs	61 (13.3)	3193 (12.3)	0.537	52 (11.8)	3299 (12.7)	0.653
Androgens	0 (0.0)	15 (0.1)	1.000	0 (0.0)	31 (0.1)	1.000
Estrogens	0 (0.0)	6 (0.0)	1.000	0 (0.0)	14 (0.1)	1.000
Calcium	20 (4.4)	617 (2.4)	0.009	14 (3.2)	618 (2.4)	0.342
Vitamin D	3 (0.7)	298 (1.1)	0.450	4 (0.9)	317 (1.2)	0.716
Bisphosphonates	8 (1.7)	280 (1.1)	0.251	10 (2.3)	240 (0.9)	0.009

older than those without, which may explain the higher incidence of hip fracture in this group.[8] In the study by de Miguel et al, although the age of the study groups was similar, comorbidity was greater among COPD patients.[26] Huang et al reported a higher risk of hip fracture among patients with COPD than those without, even after adjusting for age, sex, and comorbidities.[28] Furthermore, those authors used a follow-up period of 4 years; 1 year less than that used in the present study. Based on the present findings and those reported to date, the relationship between COPD and hip fracture therefore remains unclear.

Several factors may explain the higher incidence of hip fractures among COPD patients. On the one hand, patients with poorer lung function tend to show a greater decrease in bone mass,[29] and on the other hand, patients with COPD experience more falls than those without.[7] Finally, patients with frequent COPD exacerbations are intermittently treated with high doses of systemic corticosteroids that can contribute to the appearance of fractures.[30]

Table 3 Factors Independently Associated with Hip Fracture in the Multivariate Analysis of Individuals with and without Chronic Obstructive Pulmonary Disease (COPD)

Individuals with COPD		
	OR (95% CI)	**p value**
Age	1.09 (1.08–1.10)	<0.001
Sex, women	1.73 (1.41–2.12)	<0.001
Obesity	0.75 (0.56–0.99)	0.045
Hypertension	1.45 (1.16–1.83)	0.001
Heart failure	1.36 (1.10–1.68)	0.005
Chronic liver disease	2.62 (1.58–4.37)	<0.001
Benzodiazepines	1.45 (1.19–1.78)	<0.001
Inhaled anticholinergics	1.39 (1.13–1.70)	0.001
Individuals without COPD		
	OR (95% CI)	**p value**
Age	1.08 (1.07–1.09)	<0.001
Sex, women	1.59 (1.28–1.96)	<0.001
Obesity	0.57 (0.42–0.78)	<0.001
Hyperlipidemia	0.79 (0.64–0.96)	0.019
Heart failure	1.28 (1.01–1.61)	0.040
Stroke	1.50 (1.22–1.85)	<0.001
Chronic liver disease	2.42 (1.45–4.02)	0.001
Benzodiazepines	1.31 (1.06–1.61)	0.014

Abbreviations: CI, confidence interval; OR, odds ratio.

One surprising finding in our study was the association between hip fracture and treatment with anticholinergic bronchodilators in COPD patients. As early as 2011, Morden et al, in their analysis of data from the Veterans Administration database, reported that the use of inhaled corticosteroids was associated with hip and wrist fractures in men aged over 50 years who were newly diagnosed with COPD.[31] More recent studies reported only a modest increase in the risk of fracture, and only in patients receiving high doses of inhaled corticosteroids.[32,33] Inhaled beta-agonists, especially when administered at high doses, have also been associated with femur fractures in COPD patients.[34,35] To our knowledge, ours is the first study to report an association between antimuscarinics and the incidence of hip fracture. Given the frequency of osteoporosis and fractures in COPD patients, all pharmacovigilance studies with new bronchodilators should include fractures as an adverse effect to be monitored.

The findings of this study are strengthened by the use of a population database that includes a large number of comorbidities and medications. Nonetheless, several study limitations should be noted. First, we excluded patients with previously diagnosed osteoporosis and those that had previously experienced hip fracture. It is possible that COPD causes greater exacerbation of pre-existing osteoporosis in these particular patients, increasing the likelihood of new fractures, and that these patients were not accounted for in our analysis. Second, while studies using the FRAX tool have established that COPD patients are at high risk of hip fracture within ten years, the follow-up period in the present study was only five years. It is possible that hip fractures occur more frequently between five and ten years, and that our follow-up period was not sufficiently long to detect such fractures. In fact, the mean age of patients with hip fracture in Spain is 86.7 years, twelve years higher than in our patients.[36]

In conclusion, in our study population, COPD was not a risk factor for hip fracture within the next five years. However, studies with a longer follow-up period will be necessary to clarify any potential association. The possible association between treatment with inhaled anticholinergics and hip fracture should be monitored and further researched in patients with COPD.

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Disclosure

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