High Imminent Vertebral Fracture Risk in Subjects With COPD With a Prevalent or Incident Vertebral Fracture

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Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease caused by significant exposure to noxious particles and gases, most often tobacco smoking but also exposure to air pollution (industry, biomass fuels).1–4 COPD is characterized by progressive airflow limitation with symptoms of exertional dyspnoea, cough, and increased mucus production.

Currently, COPD is the fourth-leading cause of death worldwide and is expected to be the third-leading cause by 2030.5 Although it is primarily a respiratory disease, it also has significant extrapulmonary effects. Commonly known comorbidities include osteoporosis, cardiovascular disease, and muscle wasting, and diabetes, anemia, gastrointestinal diseases, depression, and lung cancer are frequently diagnosed in subjects with COPD.6–9

Subjects with COPD have an increased risk of osteoporosis and vertebral fractures (VFs), partly because of concomitant risk factors (older age, smoking history,9–12 inactivity,12,13 body composition12–16) but also because of disease-specific risk

Key Words: OSTEOPOROSIS; FRACTURE RISK ASSESSMENT; SCREENING

ABSTRACT

Subjects with chronic obstructive pulmonary disease (COPD) have an increased risk of vertebral fractures (VFs); however, VF incidence is largely unknown. Therefore, the aim of our study was to determine the incidence of new and/or worsening VF in subjects with COPD. Smokers and subjects with COPD (GOLD II–IV) from the ECLIPSE study with complete set of chest CT scans (baseline and 1- and 3-year follow-up) to evaluate vertebral T1 down to L1 were included. If a VF was diagnosed on the last scan, detailed VF assessment of the previous scans was performed. VFs were scored according to the method of Genant as mild, moderate, or severe. Main outcome measure was the cumulative incidence of new and/or worsening VF at subject level, within 1 and 3 years. Of 1239 subjects (mean age 61 years, 757 males [61%], 999 subjects with COPD), 253 (20.5%) had ≥1 prevalent VF. The cumulative incidence of VFs was 10.1% within 1 year and 24.0% within 3 years. After adjustment for age, sex, body mass index (BMI), pack-years, and smoking status, prevalence and incidence were similar between smokers and COPD GOLD stages. Within 1 year, 29.2% of the subjects with a prevalent VF had an incident VF, compared with 5.1% in absence of prevalent VF (hazard ratio [HR] = 5.1; 95% confidence interval [CI] 3.6–7.4) and 58.5% versus 15.0% within 3 years (HR = 3.6; 95% CI 2.9–4.6). The incidence of VF was higher with increasing number and severity of prevalent VFs. Among subjects having an incident VF within the first year, 57.3% had a subsequent VF within the next 2 years. In this study, more than half of the smokers and subjects with COPD with a prevalent VF or an incident VF within the first year sustained a subsequent VF within 3 years. The 3-year risk was even higher in the presence of multiple or severe prevalent VFs. © 2018 The Authors. Journal of Bone and Mineral Research Published by Wiley Periodicals Inc.

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factors such as systemic inflammation, glucocorticosteroid (GC) therapy, hypogonadism, and vitamin D deficiency.

The prevalence of radiographic VFs in subjects with COPD as reported in the literature is varying between 9.0% and 79%, with the prevalence of radiographic VFs in subjects with COPD increasing from 32% to 52% in a 3-year time period. However, the incidence of clinical VFs in subjects with COPD was as low as 1.3/1000 person-years to 6% over 2.6 years and 0.5% to 1.0% within 3 years.

Smokers without COPD have lower BMD and an increased risk of vertebral fractures. The prevalence of radiographic VFs in smokers as reported in the literature varied between 11% and 24%, whereas incidence of clinical VFs varied from 3% to 10% in a 30-year follow-up.

VFIs are associated with height loss, less activities in daily living, and increased mortality risk. In addition, the presence of a clinical or radiographic VF is a good predictor of subsequent VFIs and other osteoporotic fractures, even at short term, then quoted as near-term or imminent fracture risk.

There is thus a high variability in the reported prevalence of radiographic VFs in smokers and subjects with COPD and only limited data on the incidence of VFs in smokers and subjects with COPD.

Our aim was to determine the incidence of new and/or worsening VFs in smokers without COPD and subjects with COPD.

Materials and Methods

Study design and population

The ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study is a non-interventional, observational, multicenter study that was started to search underlying mechanisms of disease progression in subjects with COPD and to identify biomarkers that may serve as surrogate endpoints and therefore could measure disease progression.

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Detailed inclusion and exclusion criteria were described elsewhere. First, current or former smokers with COPD (40 to 75 years old) with GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage II (moderate: 50% ≤ forced expiratory volume in 1 second [FEV1] <80% predicted, and FEV1/FVC [forced vital capacity] <0.70), stage III (severe: 30% ≤ FEV1 <50% predicted, FEV1/FVC <0.70), or stage IV (very severe: FEV1 <30% predicted, FEV1/FVC <0.70), with a post-bronchodilator FEV1 of <80% of the predicted value, a post-bronchodilator FEV1/FVC of <0.7, and a smoking history of at least 10 pack-years (1 pack-year = 20 cigarettes per day for 1 year) were included. Subjects with COPD were recruited from the outpatient clinics of the participating centers in Europe, North America, and New Zealand.

Current or former smokers (40 to 75 years old) without COPD (with a post-bronchodilator FEV1 of >85% of the predicted value, a post-bronchodilator FEV1/FVC of >0.7) and a smoking history of at least 10 pack-years were also included. This group was recruited through site databases and other methods (adsvertisements in local newspapers and television/radio stations) where appropriate.

Main exclusion criteria were known respiratory disorders or significant inflammatory diseases other than COPD, severe α3-antitrypsin deficiency, a moderate or severe COPD exacerbation (requiring oral GC treatment, antibiotics, or hospitalization) within the 4 weeks before enrollment, and therapy with oral GC at enrollment.

Measurements

At baseline, 1-year follow-up, and 3-year follow-up, demographic information (including age, sex, height, and weight) were collected.

Chest CT scans

CT scans of the chest (120 kV peak, 40 mAs, 1.00 or 1.25-mm volumetric acquisition, General Electric [GE] or Siemens) were performed at full inspiration, at baseline and at 1-year and 3-year follow-up. CT scanners were calibrated regularly using industry and institutional standards.

Of all sagittal reformats containing the spine, the contrast was adjusted to (partly) eliminate soft tissue. Subsequently, all sagittal reformats containing the spine were superposed to create simulated lateral X-ray 2D images using Matlab version R2013a (MathWorks, Natick, MA, USA) (Supplemental Fig. S1). Images were exported in DICOM format.

Because of our interest in VFs diagnosed on adapted CT images, we only included subjects with complete availability of CT scans at baseline and 1-year and 3-year follow-up; subjects with one or more missing scans were not included in our study.

Vertebral fracture assessment

The adapted sagittal 2D CT images of the last visit (at 3-year follow-up) were visually assessed for VFs from T1 to L1.

A semiquantitative visual grading of vertebral fractures was performed, where vertebrae were graded as deformed or not deformed. Vertebral deformations were categorized using the SpineAnalyzer software (Optasia Medical, Cheddle, UK). This software automatically detects the vertebral shape and deformities on lateral images based on user-indicated points centered in the vertebrae. All of the automatically detected points of the six-point morphometry were manually checked by one operator and adjusted if necessary.

The vertebrae were classified based on height loss at posterior, middle, and/or anterior site, according to the method initially described by Genant and colleagues as no fracture (height loss <20%; grade 0), mild fracture (height loss 20% to <25%; grade 1), moderate fracture (25% to <40%; grade 2), or severe fracture (height loss >40%; grade 3).

If one or more VFs were quantitatively identified at the 3-year follow-up scan using SpineAnalyzer, the 1-year follow-up scan was also quantitatively assessed. If VFs were also quantitatively identified at the 1-year follow-up scan, the baseline scan was quantitatively assessed as well.

All images were semiquantitatively and quantitatively analyzed by one experienced reader (MJvD), who knew time sequence of the images and that there was at least one VF on later scans but who was blinded to patient characteristics and number, location, and severity of fracture(s) on other scans.

All images with one or more VFs on the 3-year scan were additionally assessed by an experienced clinician who was not
involved in the primary assessment. In case of any doubt about the nature of the deformity, a second clinician independently assessed the images. Decisions with regard to inclusion or exclusion of vertebral deformities such as Scheuermann’s disease, Schmorl’s noduli, and platyspondyly were reached by consensus.

Main outcome measure

Main outcome measure was the cumulative incidence of new (from grade 0 to grade 1, 2, or 3) and/or worsening (increase in any VF grade, eg, from grade 1 to grade 2) VFs at subject level, within 1 year and within 3 years from baseline.

Statistical analysis

The following potential confounders were determined at baseline: age, sex, weight, body mass index (BMI), smoking history (number of pack-years), and smoking status (current or former smoker).

Because we only selected subjects with complete set of CT scans, missing data were scarce and subjects with missing data were excluded from the analyses concerning those data.

Regression analysis with Cox proportional hazards models (SAS 9.3, SAS Institute, Cary, NC, USA; PHREG procedure) was used to estimate the risk of incident (new and/or worsening) VFs within 1 and within 3 years after baseline, stratified by having COPD, by GOLD stage, by the presence and number of VFs and by severity of VFs at baseline.

Furthermore, Cox proportional hazard models were used to estimate the risk of subsequent VFs within 2 years, in subjects with an incident (new and/or worsening) VF within the first year of the study, stratified by number of VFs at baseline and by severity of VFs at baseline.

In all statistical models, age and sex were included as potential confounders, and other possible confounders were included if they independently changed the beta-coefficient for having COPD by 5% or more or when consensus consisted within the team of researchers supported by evidence from literature.

Results

Of a total of 2298 ECLIPSE subjects (327 smokers and 1971 subjects with COPD), 1478 subjects had the complete set of CT scans (baseline, 1-year, and 3-year follow-up). Of these, 230 subjects were excluded because of scan quality (noise, missing slices, incorrect slice spacing; n = 156), anatomy (could not identify T1/vertebral levels, deformation of the spine; n = 14), failure of the method to edit CT scans (slice numbers not in ascending order and/or not starting at 0 or 1, problems with white balance in Matlab, or unclear adapted CT images; n = 60), or use of oral GC at baseline (n = 7). Two subjects were excluded because of vertebral deformities (one subject with platyspondyly and one subject with Scheuermann’s disease). See also Supplemental Fig. S2. In 22 subjects with VFs at 3-year follow-up, one or more individual vertebrae were excluded from the analysis because of other deformations such as Schmorl’s noduli, degenerative spondylosis, etc.

Thus, for this study, 1239 subjects (240 smokers and 999 subjects with COPD) were included. Baseline characteristics are given in Table 1. No subjects used oral GC at baseline. Oral GC use at 1-year follow-up was reported by 23 subjects (2.3% of the subjects with COPD) and by 47 subjects (4.7%) at 3-year follow-up (16 subjects [1.6%] reported GC use at both 1- and 3-year follow-up).

Table 1. Baseline Characteristics (N = 1239)

| Subjects with COPD | Smokers N = 240 | Total N = 1239 | GOLD II n = 468 | GOLD III n = 420 | GOLD IV n = 111 |
|--------------------|----------------|----------------|----------------|----------------|----------------|
| Age (years), mean ± SD | 55.0 ± 8.7 | 62.8 ± 7.0a | 62.9 ± 7.2 | 62.9 ± 6.8 | 62.2 ± 7.1 |
| Sex (M), n (%) | 139 (57.9) | 618 (61.9) | 262 (56.0) | 273 (65.0) | 83 (74.8) |
| Weight (kg), mean ± SD | 78.7 ± 14.3 | 73.9 ± 16.0a | 75.2 ± 16.1 | 73.2 ± 15.7 | 70.9 ± 15.7 |
| Fat-free mass (kg), mean ± SD | 55.9 ± 11.7 | 50.5 ± 12.3a | 51.3 ± 12.7 | 49.9 ± 11.9 | 48.9 ± 11.9 |
| Height (cm), mean ± SD | 172.1 ± 9.1 | 169.6 ± 9.0a | 169.3 ± 9.3 | 169.6 ± 8.8 | 170.8 ± 8.2 |
| BMI (kg/m²), mean ± SD | 26.5 ± 4.1 | 25.6 ± 4.6a | 26.1 ± 4.5 | 25.4 ± 4.7 | 24.2 ± 4.4 |
| FFMI (kg/m²), mean ± SD | 18.7 ± 2.7 | 17.4 ± 3.2a | 17.7 ± 3.2 | 17.2 ± 3.2 | 16.6 ± 3.3 |
| FEV1, post-dose (L), mean ± SD | 3.39 ± 0.75 | 1.39 ± 0.52a | 1.77 ± 0.46 | 1.14 ± 0.26 | 0.72 ± 0.16 |
| FEV1, post-dose (%predicted), mean ± SD | 109.4 ± 11.8 | 49.6 ± 15.7a | 63.8 ± 8.3 | 40.5 ± 6.0 | 24.8 ± 3.6 |
| FVC, post-dose (L), mean ± SD | 4.33 ± 0.98 | 3.13 ± 0.91a | 3.43 ± 0.92 | 2.98 ± 0.81 | 2.41 ± 0.71 |
| FVC, post-dose (%predicted), mean ± SD | 113.9 ± 13.4 | 89.7 ± 19.4a | 100.0 ± 15.7 | 84.7 ± 16.4 | 65.5 ± 14.9 |
| FEV1/FVC, post-dose (%predicted), mean ± SD | 101.4 ± 6.6 | 58.5 ± 14.7a | 68.8 ± 11.6 | 51.7 ± 10.3 | 41.1 ± 8.1 |
| Smoking status | | | | | |
| Current smoker, n (%) | 153 (63.8) | 371 (37.1a) | 184 (39.3) | 156 (37.1) | 31 (27.9) |
| Former smoker, n (%) | 87 (36.3) | 628 (62.9a) | 284 (60.7) | 264 (62.9) | 80 (72.1) |
| Pack-years, mean ± SD | 31.6 ± 20.2 | 46.1 ± 25.0a | 44.9 ± 26.7 | 46.9 ± 22.8 | 47.8 ± 25.6 |
| VF at baseline (yes), n (%) | 38 (15.8) | 153 (15.8) | 153 (15.8) | 153 (15.8) | 153 (15.8) |

COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; BMI = body mass index; FFMI = fat-free mass index; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; VF = vertebral fracture.

*p < 0.001 versus smokers without COPD.

*p < 0.005 versus smokers without COPD.

*p < 0.05 versus smokers without COPD.
Table 2. Prevalence of Vertebral Fractures Among Smokers and Subjects With COPD at Baseline, Stratified by Number and by Severity

|                      | Smokers  | Total   | GOLD II | GOLD III | GOLD IV |
|----------------------|----------|---------|---------|----------|---------|
|                      | (N = 240)| (N = 999)| (n = 468)| (n = 420)| (n = 111)|
| By number of VFs     |          |         |         |          |         |
| No VF                | 202      | 84.2    | 782     | 78.4ab   | 367     | 77.8    |
| 1 VF                 | 28       | 11.7    | 111     | 11.1     | 52      | 11.2    |
| ≥2 VF                | 10       | 4.2     | 104     | 10.4ab   | 47      | 10.1    |
| By severity of VFs   |          |         |         |          |         |
| Grade 0              | 202      | 84.2    | 782     | 78.4ab   | 367     | 77.8    |
| Grade 1              | 25       | 10.4    | 95      | 9.5      | 52      | 11.2    |
| Grade 2              | 13       | 5.4     | 87      | 7.3      | 34      | 7.3     |
| Grade 3              | 0        | 0.0     | 33      | 3.3ab    | 13      | 2.8     |
| Missing number of VF at baseline: 2 COPD (2 GOLD II); missing highest VF grade at baseline: 2 COPD (2 GOLD II).

Prevalence of vertebral fractures

At baseline, 20.5% of the participants had a prevalent VF; 15.8% of the smokers and 21.6% of the subjects with COPD (Table 2). After adjustment for age and sex, having at least one VF was not significantly different between smokers and subjects with COPD or between GOLD stages.

A significantly larger proportion of the men had a prevalent VF (24.5% in men versus 14.1% in women, p < 0.001), and prevalence of VFs was associated with older age (p < 0.001).

Incidence of vertebral fractures, stratified by presence and severity of COPD

The cumulative incidence of VFs within 1 year was 7.5% among smokers and 10.6% among subjects with COPD (Table 3), and after 3 years 20.0% and 24.9%, respectively. After adjustment for age, sex, BMI, pack-years, and smoking status, the risk of incident VF was not significantly different between smokers and subjects with COPD.

Incidence of vertebral fractures, stratified by prevalent vertebral fractures

Apart from age and sex, the presence of a prevalent VF at baseline was a major risk factor for incident VFs. After 1 and after 3 years, the incidence of VFs was 29.2% and 58.5%, respectively, in subjects with a prevalent VF compared with 5.1% and 15.0%, respectively, in subjects without a prevalent VF (1-year HR = 5.1, 95% CI 3.6–7.4; 3-year HR = 3.6, 95% CI 2.9–4.6; adjusted for age,

Table 3. Risk of Incident Vertebral Fractures Within 1 and Within 3 Years, Stratified by COPD and by GOLD Stages Compared With Smokers

|                      | Incident within first year | Risk of incident VF within first year | Incidence within 3 years | Risk of incident VF within 3 years |
|----------------------|---------------------------|--------------------------------------|--------------------------|-----------------------------------|
|                      | n  | % | HR (95% CI) | adj. HR (95% CI) | n  | % | HR (95% CI) | adj. HR (95% CI) |
| Smokers (N = 240)   | 18 | 7.5 | — | — | 48 | 20.0 | — | — |
| COPD (N = 999)      | 106 | 10.6 | 1.4 (0.86–2.34) | 1.0 (0.58–1.70) | 249 | 24.9 | 1.2 (0.92–1.70) | 1.0 (0.69–1.35) |
| COPD by GOLD        |          |         |         |          |          |         |         |          |
| GOLD II (n = 468)   | 43 | 9.2 | 1.2 (0.71–2.14) | 0.9 (0.51–1.66) | 109 | 23.3 | 1.2 (0.83–1.64) | 0.9 (0.64–1.33) |
| GOLD III (n = 420)  | 43 | 10.2 | 1.4 (0.79–2.37) | 0.9 (0.52–1.68) | 106 | 25.2 | 1.3 (0.90–1.78) | 1.0 (0.66–1.39) |
| GOLD IV (n = 111)   | 20 | 18.0 | 2.4 (1.27–4.54) | 1.5 (0.77–3.02) | 34 | 30.6 | 1.5 (0.99–2.38) | 1.1 (0.71–1.81) |
| Trend n.s.          | (p = 0.777) |        |        |        | Trend n.s. | (p = 0.273) |        |        |
| Trend n.s.          | (p = 0.052) |        |        |        | Trend n.s. | (p = 0.617) |        |        |

COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; VF = vertebral fracture; HR = hazard ratio; adj. HR = hazard ratio adjusted for age, sex, body mass index, pack-years, and smoking status; CI = confidence interval. Missing first year: 5 subjects with COPD (4 GOLD II, 1 GOLD III); missing 3 years: 2 COPD (1 GOLD II, 1 GOLD III). Note: the trend for incidence by group is based on “smokers,” “GOLD II,” “GOLD III,” or “GOLD IV.”
The incidence of VFs was related to the number and severity of baseline VFs. As an example, the 3-year incidence was 68.4% in subjects with ≥2 VFs at baseline (adj. HR = 4.2, 95% CI 3.2–5.6) and 75.8% of subjects with a grade 3 VF at baseline (adj. HR = 4.3, 95% CI 2.7–6.8).

In this model including prevalent VFs at baseline, none of the confounders was significantly associated with the risk of incident VF, except for sex and the risk of incident VF within 1 year (men compared with women, 1-year HR = 1.57, 95% CI 1.03–2.39; 3-year HR = 1.20, 95% CI 0.93–1.55).

Incidence of subsequent VFs within the 2 years after an incident VF

A total of 124 subjects had an incident VF within the first year. Of these 124 subjects, 57% (71 subjects: 26 without prevalent VFs and 45 with 1 or more prevalent VFs at baseline) had a subsequent VF within the next 2 years (Table 4). In these subjects, the incidence of subsequent VFs within the 2 years after an incident VF was not significantly related to the presence, number, and severity of prevalent VFs at baseline.

None of the confounders (age, sex, BMI, pack-years, smoking status, or having COPD) were significantly associated with the risk of incident VFs in the 2 years after an incident VF.

Of the 124 subjects with incident VFs within the first year, 3 subjects (2.4%) reported the use of oral GC at 1-year follow-up. Adding the use of oral GC to the model as a confounder did not influence the results (data not shown).

**Discussion**

More than half of the current or former smokers and subjects with COPD with a prevalent VF at baseline or an incident VF within the first year sustained a subsequent VF within 2 (after an incident VF) or 3 (after a prevalent VF) years. Three-year incident VF risk was 3.6 times higher in those with a prevalent VF than those without a prevalent VF and independent of age, BMI, and...
sex (except for a higher 1-year incidence in men). The risk of incident VFs increased with the number and severity of prevalent VFs but was similar between smokers and subjects with COPD and among COPD GOLD stages.

Comparison to published research

The prevalence of VFs in our study population (21.6% of the COPD subjects had \( \geq 1 \) VF at baseline and 33.5% at 3-year follow-up) was at the somewhat lower range compared with prevalence of most COPD reports found in literature (mostly 24% to 45\% \( ^{23-30,32} \) with outliers of 9.0\% \( ^{15} \) and 79.4\% \( ^{31} \)). This could probably be explained by the fact that the subjects in this study were not using oral GC at baseline because of study design (subjects using oral GC at baseline were excluded, and only 23 and 47 subjects, respectively, reported oral GC use at 1-year and 3-year follow-up), whereas in most (12\% to 86\% \( ^{15,27-29,32} \) GC use) but not all (2.2\% to 4.5\% \( ^{23,24,28} \) GC use) studies, the percentage of subjects using GCs was considerably higher.

Furthermore, we measured vertebrae T1 to L1 and therefore had no information regarding VFs in the lumbar vertebrae except L1. McEvoy and colleagues \( ^{33} \) showed that 16.5\% of the male COPD patients in their study population had a VF in the lumbar spine and 49.0\% in the thoracic spine and that the risk of VFs was highest in patients using GC.

In a large cohort of COPD patients in Italy, Nuti and colleagues \( ^{15} \) found a relationship between COPD severity by means of GOLD stages and prevalence of \( \geq 1 \) VF, especially in male subjects. In a multivariate model, they showed an association between VFs and age, fracture history after the age of 50 years, BMI, COPD severity, and GC treatment; however, they did not report VF incidence. In our study, we could not show a significant association between prevalence of VFs and GOLD stages (adjusted for age and sex). However, our study population was younger, all subjects had a significant smoking history (mean of 43.3 ± 24.8 pack-years, with a minimum of 10 pack-years), whereas in the study by Nuti and colleagues, 13.3\% of men and 55.1\% of women were non-smokers and subjects with GOLD stage I were not included.

Another remarkable finding was that there was no difference in VF incidence between smokers and subjects with COPD. Our participants had a significant smoking history (46 pack-years for the COPD group, 32 for the smokers), indicating that smoking rather than COPD is a major risk factor for VFs \( ^{11,38,39} \).

In a group of 90 COPD patients (69 ± 1 years old, 60\% male), Graat-Verboom et al. \( ^{32} \) showed an increase of prevalent VFs from 32\% to 52\% within three years (63\% increase). In our study population, prevalence of VFs increased from 20.4\% at baseline to 24.5\% at 1-year and 32.4\% at 3-year follow-up (59\% increase), indicating a similar increase.

We showed that presence, number, and severity of prevalent VFs were associated with risk of incident VFs, which is in line with multiple studies showing that prevalent VFs are an important independent risk factor for subsequent VFs \( ^{43-45,54} \) and several other osteoporotic fractures. \( ^{43,44,47,48,54} \) However, the incident 1-year risk was much higher than reported in postmenopausal women. \( ^{45} \) In postmenopausal women selected on the basis of a prevalent VF, low BMD at the femoral neck, or risk factors for hip fracture, the 1-year VF incidence was 1.9\% in women without prevalent VFs, 9.9\% in women with prevalent VFs of unknown date, and 19.2\% in women with an incident VF.

Given the VF prevalence of 21.6\% in COPD subjects and the high risk of subsequent VFs in those with a prevalent or incident VF, we propose to systematically evaluate the presence of VFs when these patients have chest X-ray or chest CTs made for pulmonary evaluation. Improvement in patient care can be achieved by increasing awareness among pulmonologists and radiologists about the clinical importance for recognizing VFs. Patients with VFs should be further evaluated and treated.
according to local osteoporosis and fracture prevention guidelines.

Limitations

This study has several limitations. First, there is a possibility of a selection bias. Because we only included subjects with complete availability of all three CT scans, we have only selected the surviving subjects and subjects willing and able to complete the study. The subjects included in our subcohort were somewhat younger (61.3 ± 8.0 versus 62.3 ± 7.9 years old), were less often males (61.1% versus 62.6%), had lower BMI (25.8 ± 4.5 versus 26.6 ± 5.5 kg/m²), and were more often smokers without COPD (19.4% versus 14.2%) compared with the total ECLIPSE population. The percentage of current smokers was higher (42.3% versus 39.9%), but the mean number of pack-years was lower (43.3 ± 24.8 versus 46.2 ± 27.1) compared with the total ECLIPSE population (Supplemental Table S3).

Second, the subjects in this study, especially those with COPD, were selected based on not using oral GC at baseline, and subjects with COPD were selected from outpatient clinics, which limits the applicability of our results to subjects with COPD in general. Besides, the group including subjects with very severe COPD (GOLD stage IV) was smaller than the other groups (111 compared with 468 subjects with GOLD II and 420 subjects with GOLD III), which possibly may have resulted in a limited statistical power when estimating the association of GOLD stage IV with the risk incident VFs in this specific group.

Furthermore, although 524 (42.3%) of all subjects were current smokers, there was only a limited number of current or former smokers without COPD included in our study (n = 240), which limits the generalizability of these results to the general population of heavy (current or former) smokers without COPD. In addition, the participating research centers were located in North America, Europe, and New Zealand, and therefore the results are not applicable to populations of other ethnic origin.

Although the incidence of VFs within 3 years after a prevalent VF at baseline (148 of 253 subjects, 58.5%) or within 2 years after an incident VF within the first year (26 of 50 subjects, 52.0%) is very high, it should be noted that the sample size of subjects with a prevalent VF (n = 253) or incident VF within the first year in absence of prevalent VFs (n = 50) is limited.

We assessed VFs on images based on CT scans and used morphometry software to assess VFs, which possibly has resulted in a more sensitive method to assess VFs than by visual inspection of X-ray images. In the absence of beam divergence and with use of morphometry software, small height changes can be detected that could have resulted in higher VF grade, thereby possibly making CT in combination with morphometry software more sensitive.

Lastly, we only have assessed VFs between T1 and L1, because of the nature of our scans and therefore cannot say anything about prevalence and/or incidence of VFs in the lower lumbar part of the spine. It is possible that not assessing L2 to L3 has resulted in an understimation because of missing prevalent and/or incident VFs in this lumbar area. However, according to literature, most VFs occur in the mid-thoracic and thoracolumbar area of the spine, which are both visible on chest CT scans.

In conclusion, in this 3-year follow-up study, we showed that more than half of the heavy current or former smokers and COPD subjects with a prevalent VF at baseline or an incident VF within the first year sustained a subsequent VF within the follow-up period (3 years after a prevalent VF, 2 years after an incident VF). This imminent VF risk was even higher in the presence of multiple or severe VFs at baseline.

Disclosures

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