Osteoporosis and fracture risk associated with inhaled corticosteroid use among Swedish COPD patients: the ARCTIC study

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COPD patients are at high risk of fractures and osteoporosis. ICS use, especially at high doses, increases this risk further. It is therefore important to pinpoint which patients benefit from ICS to reduce unnecessary exposure to ICS-associated risks. https://bit.ly/34V3OeW

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ABSTRACT The effect of inhaled corticosteroids (ICS) on the risk of osteoporosis and fracture in patients with chronic obstructive pulmonary disease (COPD) remains uncertain. The aim of this study was to assess this risk in patients with COPD.

Electronic medical record data linked to National Health Registries were collected from COPD patients and matched reference controls at 52 Swedish primary care centres from 2000 to 2014. The outcomes analysed were the effect of ICS on all fractures, fractures typically related to osteoporosis, recorded osteoporosis diagnosis, prescriptions of drugs for osteoporosis and a combined measure of any osteoporosis-related event. The COPD patients were stratified by the level of ICS exposure.

A total of 9651 patients with COPD and 59454 matched reference controls were analysed. During the follow-up, 19.9% of COPD patients had at least one osteoporosis-related event compared with 12.9% of reference controls ($p<0.0001$). Multivariate analysis in the COPD population demonstrated a dose–effect relationship, with high-dose ICS being significantly associated with any osteoporosis-related event (risk ratio 1.52 (95% CI 1.24–1.62)), while the corresponding estimate for low-dose ICS was 1.27 (95% CI 1.13–1.56) compared with COPD patients not using ICS. A similar dose-related adverse effect was found for all four of the specific osteoporosis-related events: all fractures, fractures typically related to osteoporosis, prescriptions of drugs for osteoporosis and diagnosis of osteoporosis.

We conclude that patients with COPD have a greater risk of bone fractures and osteoporosis, and high-dose ICS use increased this risk further.

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Data availability: The data for this study were obtained from electronic medical records in primary care and the Swedish National Health Register. Restrictions apply to the availability of these data, which were used under licence for the current study and so are not publicly available. Data are, however, available from IQVIA Solutions, Solna, Sweden (E-mail: binekjoeller.bjerregaard@iqvia.com), upon reasonable request and with permission of the Swedish National Health Register.

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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality worldwide. Current guidelines recommend the use of inhaled corticosteroids (ICS) in patients who are at high risk of exacerbations and elevated blood eosinophil levels or patients with asthma–COPD overlap [1, 2]. However, in many countries, ICS are being prescribed to >60% of total COPD patients who do not fulfil these criteria [3, 4].

ICS use, especially at a high dose, in COPD patients is associated with adverse events such as pneumonia [5–7]. There are also indications that ICS use in COPD is related to other adverse effects, such as an increased risk of glaucoma, cataracts, osteoporosis, diabetes, candidiasis, hoarseness and bruising [8, 9]. Osteoporosis with resulting fractures is a significant comorbidity among COPD patients [10]. Multiple factors, such as old age, inactivity, smoking and systemic inflammation, partly explain the association between COPD and osteoporosis [11, 12]. In 2013, Loke *et al.* [13] published a meta-analysis of randomised controlled trials (RCTs) and observational studies, and concluded that long-term ICS use (budesonide and fluticasone) is associated with a modest but statistically significant increased risk of fractures among COPD patients.

Reports published after 2013 give a mixed picture, with one study showing that high- but not low-dose ICS treatment is associated with a larger decrease in bone mineral density [14], while another study indicated that ICS use actually protects against osteoporosis in females with COPD [15]. A recent review of 17 RCTs by Caramori *et al.* [16] concluded that the relationship between ICS use and bone fracture incidence in stable COPD patients remains unclear. Similar results were reported in the KRONOS trial, where no difference was observed for change in bone mineral density between patients treated with an ICS combination compared with those treated with long-acting muscarinic antagonists (LAMAs) plus long-acting β_2-agonists (LABAs) [17].

The objective of this real-world study was to analyse data of Swedish primary care patients with COPD to identify risk factors for osteoporosis and fractures, and determine their relationship with ICS use. Additional objectives were to assess how ICS dose, female sex, age, presence of concurrent asthma and other comorbidities affected the risk of osteoporosis and fractures in patients with COPD.

Methods

Study design

ARCTIC was a large, real-world, retrospective, Swedish cohort study conducted in 18 586 eligible, primary care, COPD patients [6, 18–20]. Approval was obtained from the local Ethical Regional Board in Uppsala, Sweden, on December 11, 2014 (number 2014-397), for accessing the National Health Register and for recruiting primary care centres to the study. An amendment specifying additional analysis was approved by the Ethical Regional Board in Uppsala on October 6, 2017. Data from all records were deidentified; therefore, the ethics committee did not require patient consent. Electronic medical record (EMR) data were collected from patients with physician-diagnosed COPD and reference patients at 52 primary care centres across Sweden between 2000 and 2014 using established software (Pygargus Customised eXraction Program; CXP 3.0 [6, 18–20]), and included age, sex, prescriptions (according to World Health Organization Anatomical Therapeutic Chemical (ATC) codes), physician's diagnoses (according to International Classification of Diseases, Tenth Revision (ICD-10) codes), spirometry measurements (forced expiratory volume in 1 s), laboratory tests, healthcare professional visits and referrals. The centres covered urban and rural sites of varying sizes across Sweden. EMR data were linked by the Swedish National Board of Health and Welfare using individual patient identification (ID) numbers to national registry data sources (patient IDs were pseudonymised). These data sources included 1) the National Patient Register, which contains data related to diagnosis from secondary care (ICD-10 code and associated position), including surgery, sex, age, region, hospital visits, specialty visits, hospital admissions and discharges, and medical procedures and surgeries performed in inpatient and outpatient specialist settings; 2) the National Prescription Register (from 2005), which tracks all details of all medications dispensed from community pharmacies (ATC codes), including brand name, prescription date, dose, strength, pack size, specialty of the prescriber and costs associated with the drug prescription; and 3) the Cause of Death Register, which holds information related to sex, date of death and underlying cause of death.

Study patients

The study population consisted of patients aged ⩾40 years who had received a physician's diagnosis of COPD (ICD-10 code: J44) with or without asthma (ICD-10 code: J45/J46) in a primary care setting (EMR database) or in a hospital setting (according to the National Patient Register). Patients' diagnoses were defined by ICD codes, while lung function was used to assess the degree of airflow limitation based on data collected from EMRs. Comorbidities were defined by the recorded ICD-10 diagnoses from primary

and secondary care settings. The study index date constituted the time of the first recorded physician's diagnosis of COPD during the enrolment time frame. An age- and sex-matched reference population was selected from the same primary care centres, excluding those who had a diagnosis of COPD and/or asthma. A random date between the start and end of the observation period for the reference patients was selected as the index date for the reference population. In order to focus exclusively on the effects of ICS, patients with more than one dispensation of oral corticosteroids (OCS) at any time-point from 2000 to 2014 were excluded from the study. Each COPD patient was matched with a mean of seven (maximum of 10) reference patients, depending on the size of the age group, to allow for comparisons in the associated risks for osteoporosis, with emphasis on ICS use. Patients in the control group with any use of ICS and/or OCS were excluded. ICS use was established using the ATC code R03BA from the EMRs and the drug prescription registry. The dispensed amounts of different types of ICS (budesonide, fluticasone propionate, beclomethasone, rest of the R03BA group and all steroid combinations in the R03AK group) were converted to budesonide equivalents. COPD patients were stratified by the level of ICS exposure after the index date until an event (high dose ($\geqslant$640 μg·day^{-1} budesonide or equivalent), low dose (<640 μg·day^{-1} budesonide or equivalent) and no ICS).

Outcomes

The outcomes analysed were the association of ICS with 1) all fractures, 2) fractures typically related to osteoporosis, 3) recorded osteoporosis diagnosis, 4) prescriptions of drugs for osteoporosis and 5) any osteoporosis-related event, *i.e.* any outcome from 2) to 4). The diagnosis of osteoporosis-related events was collected from primary care and secondary care settings. The primary outcome of interest was the incidence of fractures typically related to osteoporosis identified using the following ICD-10 codes: S02, S12, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10, T12, M80 and M84. Two fractures recorded on the same day were treated as one event. For an osteoporosis-related event, patients with osteoporosis at the index date were excluded.

Statistical analysis

A sample size calculation conducted prior to the study indicated that 13 800 patients were required to detect a 4% difference between groups, with a power of 80% and an α-level of 5% in the two-tailed test. PC SAS for Windows version 9.4 (SAS Institute, Cary, NC, USA) was used for statistical analysis. Patient demographics were described for both patients with COPD and reference controls. No immortal time bias was identified in our study setup. The statistical reference group for analysis was patients without COPD who were not taking ICS and/or OCS at any time during the study period, except when analysing ICS use, where the reference group included COPD patients not using ICS. The analyses were stratified based on age, sex, level of ICS exposure (high, low and no ICS) and disease status (presence of asthma and other comorbidities). We also compared the incidence of osteoporosis-related events between the COPD and non-COPD populations using 1:1 propensity score matching on age, sex, comorbid diseases and number of outpatient visits.

The variables were also merged into four multivariate models with the aforementioned five outcomes as dependent variables and ICS exposure, age, sex and comorbidities as independent variables. ANOVA was performed with the number of events during the follow-up as the outcome and the ICS dose group as the independent variable, adding sex and age class as covariates. From this adjusted model, the rate ratios between groups were calculated. It was expected that prescriptions of drugs for the treatment of osteoporosis would be more frequent than recorded osteoporosis diagnoses. Therefore, to ensure all incidences of osteoporosis were captured, the time to first prescription of a drug for osteoporosis, such as bisphosphonates, selective oestrogen receptor modulators, denosumab, parathyroids and oestrogen (ATC codes: M05BA, M05BB, M05BX, H05AA and G03XC), was identified from EMRs and the drug registry.

Results

Patient demographics

Of the 202 397 patients identified from EMRs, 9651 patients with COPD were eligible for inclusion in this study, matched with 59 454 reference controls (figure 1). Baseline demographics of the study population are summarised in table 1. Patients in the COPD population were older than those in the reference population (70 *versus* 65 years; p<0.0001) and had significantly higher comorbidities compared with reference controls, all of which were adjusted for in the comparative analyses (table 1). While the populations were well matched for age and sex, the number of reference patients matched to a COPD patient was not the same across all age groups, leading to a difference in these variables at baseline. Matching using propensity scoring of all osteoporosis resulted in two populations with an equal sex distribution and a smaller difference in age between the COPD and reference group (supplementary table S1).

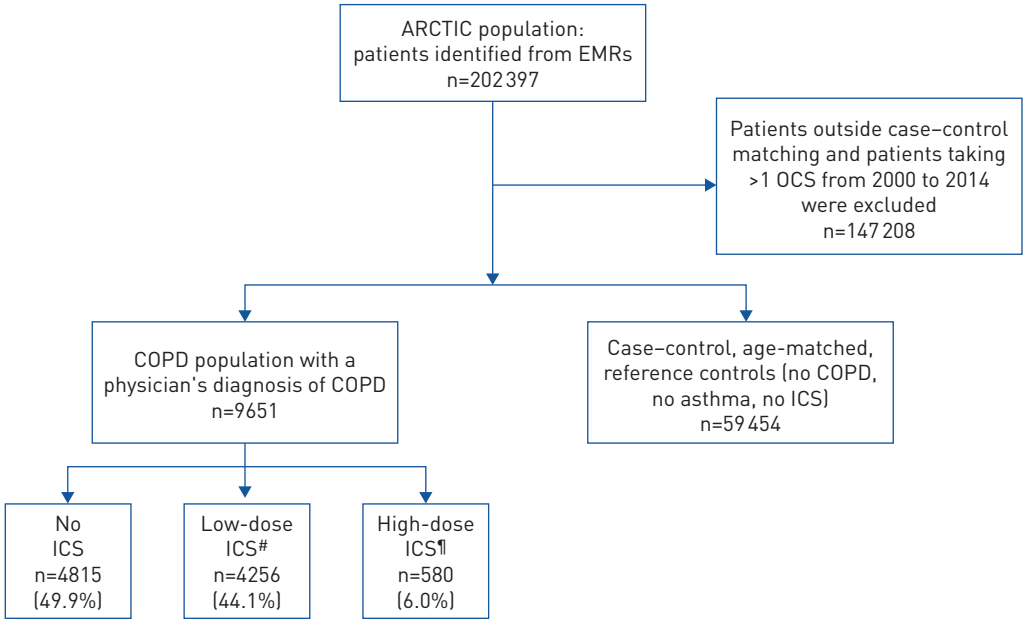

FIGURE 1 Study cohorts and criteria for patients with a physician's diagnosis of chronic obstructive pulmonary disease (COPD). EMR: electronic medical record; OCS: oral corticosteroids; ICS: inhaled corticosteroids. #: low-dose ICS <640 µg·day^{-1}; ¶: high-dose ICS ⩾640 µg·day^{-1}.

Medication use

Overall, 44.1% of patients were receiving low-dose ICS, while 6.0% were receiving high-dose ICS (figure 1). During the study period, the majority of patients had used both budesonide and fluticasone propionate (46.0%), followed by only budesonide (41.3%) and only fluticasone propionate (12.7%).

Risk of osteoporosis-related events

The mean±SD follow-up time was 5.13±4.00 and 5.34±3.95 years in the COPD and reference populations, respectively. During the follow-up (2000–2014 post-index date), 19.9% of COPD patients had at least one

TABLE 1 Baseline demographics for chronic obstructive pulmonary disease (COPD) patients and reference controls

	COPD population	Reference population, without ICS use	p-value
Subjects	9651	59 454	
Age years	69.5±11.3	65.3±12.1	<0.0001
Female	4921 (51.0)	31 646 (53.2)	<0.0001
Comorbidity#			
Asthma (J45)	867 (9.0)	419 (0.7)	<0.0001
Cardiovascular diseases (I00–I99)	3932 (40.7)	13 140 (22.1)	<0.0001
Cerebrovascular diseases (I60–I69)	464 (4.8)	1635 (2.8)	<0.0001
Depression (F32+F33)	515 (5.3)	1339 (2.3)	<0.0001
Diabetes type 2 (E10)	220 (2.3)	1021 (1.7)	0.0001
Diabetes type 3 (E11+E13)	744 (7.7)	2625 (4.4)	<0.0001
Heart failure (I209+I25+I50)	1512 (15.7)	3332 (5.6)	<0.0001
Hyperlipidaemia (E78.5)	230 (2.4)	605 (1.0)	<0.0001
Hypertensive diseases (I10–I15)	2324 (24.1)	7676 (12.9)	<0.0001
Ischaemic heart diseases (I20–I25)	1086 (11.3)	2818 (4.7)	<0.0001
Renal disease (N17+N18)	156 (1.6)	303 (0.5)	<0.0001
Rheumatoid arthritis (M05+M06)	53 (0.6)	245 (0.4)	0.0566
Sleep apnoea (G473)	81 (0.8)	319 (0.5)	0.0003

Data are presented as n, mean±SD or n (%), unless otherwise stated. ICS: inhaled corticosteroid. #: comorbidities 2 years prior to COPD diagnosis date (according to International Classification of Diseases, Tenth Revision codes).

osteoporosis-related event compared with 12.9% of the reference controls (p<0.0001). The percentage of patients with at least one fracture or osteoporosis-related event is presented in figure 2. A higher incidence for all outcomes was observed in the COPD population compared with the reference population irrespective of ICS use. A dose–response relationship for ICS was demonstrated for most of the outcomes and the highest incidence was found in the COPD group using high-dose ICS (figure 2). A higher incidence of all osteoporosis events was also found for the COPD group compared with the reference group after propensity score matching (supplementary table S2).

Fractures typically related to osteoporosis

The rate ratios for the fractures typically related to osteoporosis are presented in table 2. COPD was associated with an increased risk of these fractures irrespective of ICS use. The risk was 37% higher among COPD patients using high-dose ICS compared with reference controls. Furthermore, the risk was found to be higher in females and elderly patients.

When the COPD and reference groups were selected through propensity score matching, a significant association was found between having COPD, ICS treatment and fractures typically related to osteoporosis; however, no such association was observed with respect to age and sex (supplementary table S3).

Multivariate analysis

A multivariate analysis conducted to identify independent predictors of osteoporosis events in patients with COPD showed that several variables, including ICS use, female sex, older age and presence of comorbidities (except sleep apnoea and hyperlipidaemia), were significantly and independently associated with osteoporosis-related events (table 3). Diabetes was positively associated with fractures but negatively with having a diagnosis of and treatment for osteoporosis. High-dose ICS was significantly associated with a 52% increase in any osteoporosis-related event, while low-dose ICS had a small but significantly higher risk of osteoporosis-related events. In addition, COPD patients using high-dose ICS had a more than 2-fold increase in the risk of prescriptions of drugs for osteoporosis *versus* patients not using ICS.

As in the reference population, the results of the analysis demonstrated that age and female sex were independently associated with an increased rate of outcomes, including fractures, diagnosis of osteoporosis and prescriptions of drugs for osteoporosis in COPD patients.

Discussion

Our results showed that the risk of osteoporosis was higher in patients with COPD than in subjects without COPD, and that a dose–effect relationship exists between ICS use and osteoporosis in the COPD groups.

Irrespective of ICS use, the risk of osteoporosis was higher in all COPD groups compared with the reference controls. These results are supported by previously published studies [21–25], and also in two recent systematic reviews and meta-analyses [10, 26].

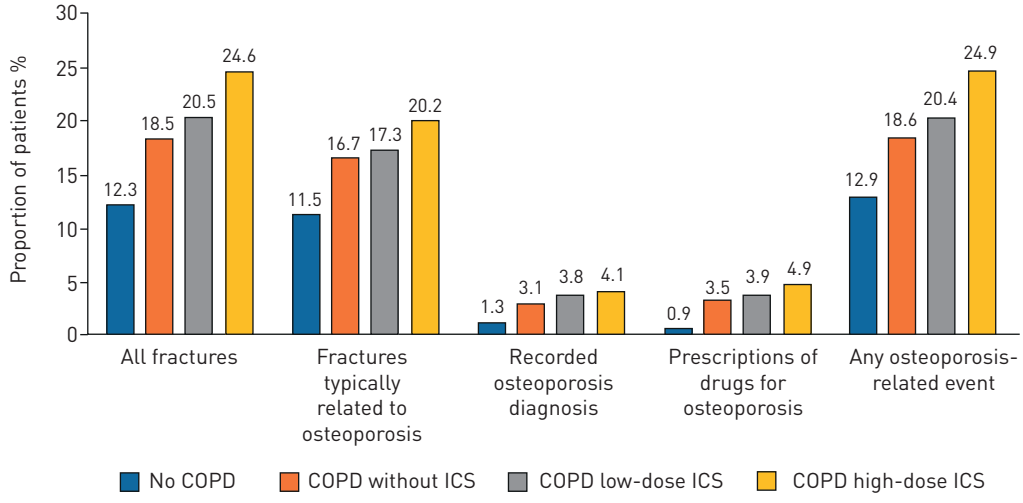

FIGURE 2 Association between chronic obstructive pulmonary disease (COPD), inhaled corticosteroid (ICS) use and osteoporosis-related events.

TABLE 2 Rate ratios (95% CI) for fractures typically related to osteoporosis

Sex	
Male	Reference
Female	1.36 (1.23–1.50)
Age group years	
<50	Reference
50– <60	1.07 (0.97–1.19)
60– <70	1.03 (0.93–1.14)
70– <80	1.12 (1.01–1.24)
>80	1.17 (1.06–1.30)
COPD[#]	
Reference controls	Reference
No ICS	1.16 (1.04–1.57)
Low-dose ICS	1.28 (1.17–1.63)
High-dose ICS	1.37 (1.21–1.51)

COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroids. [#]: adjusted for age, sex and comorbidities during the follow-up.

TABLE 3 Rate ratios[#] (95% CI) for osteoporosis-related outcomes in chronic obstructive pulmonary disease (COPD) patients

	All fractures	Fractures typically related to osteoporosis	Recorded diagnosis of osteoporosis	Prescriptions of drugs for osteoporosis	Any osteoporosis-related event
ICS					
No	Reference	Reference	Reference	Reference	Reference
Low dose	1.19 (1.05–1.21)	1.13 (1.02–1.17)	1.28 (1.22–1.33)	1.43 (1.24–1.56)	1.27 (1.13–1.56)
High dose	1.26 (1.23–1.39)	1.16 (1.05–1.24)	1.41 (1.26–1.53)	2.31 (2.12–2.50)	1.52 (1.24–1.82)
Sex					
Male	Reference	Reference	Reference	Reference	Reference
Female	1.79 (1.65–1.96)	1.62 (1.50–1.75)	5.44 (5.22–5.67)	6.71 (6.52–6.90)	2.08 (1.88–2.30)
Age group years					
<50	Reference	Reference	Reference	Reference	Reference
50– <60	1.03 (0.86–1.24)	1.00 (0.85–1.18)	1.62 (1.48–1.77)	3.13 (2.95–3.33)	1.11 (0.90–1.37)
60– <70	1.00 (0.84–1.19)	0.90 (0.77–1.06)	2.41 (2.22–2.62)	8.04 (7.59–8.52)	1.20 (0.98–1.46)
70– <80	1.18 (0.99–1.40)	1.04 (0.89–1.22)	2.15 (1.98–2.34)	8.53 (8.05–9.04)	1.39 (1.13–1.70)
>80	1.23 (1.02–1.47)	1.15 (0.98–1.36)	1.76 (1.61–1.92)	6.94 (6.54–7.37)	1.39 (1.13–1.71)
Comorbidities[¶]					
Asthma	1.28 (1.17–1.40)	1.31 (1.21–1.42)	1.01 (0.97–1.05)	1.06 (1.03–1.09)	1.22 (1.10–1.35)
Cardiovascular diseases	1.42 (1.29–1.57)	1.41 (1.29–1.54)	1.84 (1.76–1.93)	1.58 (1.53–1.64)	1.58 (1.42–1.77)
Cerebrovascular diseases	1.40 (1.27–1.54)	1.44 (1.32–1.58)	1.13 (1.08–1.19)	1.14 (1.10–1.17)	1.35 (1.21–1.52)
Depression	1.67 (1.52–1.84)	1.64 (1.50–1.80)	1.76 (1.68–1.85)	1.35 (1.31–1.40)	1.58 (1.41–1.77)
Diabetes type 1	1.24 (1.07–1.43)	1.36 (1.19–1.55)	0.59 (0.55–0.64)	0.65 (0.62–0.68)	1.19 (1.01–1.42)
Diabetes type 2	1.14 (1.04–1.26)	1.21 (1.10–1.32)	0.71 (0.67–0.74)	0.72 (0.70–0.75)	1.06 (0.95–1.19)
Heart failure	1.47 (1.36–1.60)	1.44 (1.34–1.55)	1.29 (1.24–1.34)	1.15 (1.11–1.18)	1.46 (1.33–1.60)
Hyperlipidaemia	0.99 (0.88–1.11)	1.02 (0.92–1.14)	1.31 (1.24–1.39)	0.73 (0.70–0.76)	1.00 (0.87–1.14)
Hypertension	1.15 (1.07–1.25)	1.19 (1.11–1.28)	1.16 (1.12–1.20)	1.39 (1.35–1.42)	1.24 (1.13–1.36)
Ischaemic heart disease	1.38 (1.27–1.51)	1.40 (1.29–1.51)	1.44 (1.38–1.50)	1.31 (1.27–1.34)	1.41 (1.27–1.56)
Renal disease	1.38 (1.20–1.58)	1.40 (1.24–1.59)	1.97 (1.85–2.11)	1.14 (1.09–1.19)	1.36 (1.16–1.59)
Rheumatoid arthritis	1.50 (1.11–2.04)	1.44 (1.08–1.91)	3.06 (2.64–3.56)	0.94 (0.85–1.04)	1.67 (1.16–2.39)
Sleep apnoea	0.78 (0.64–0.94)	0.82 (0.70–0.98)	0.57 (0.52–0.62)	0.78 (0.73–0.83)	0.76 (0.61–0.94)

ICS: inhaled corticosteroids. [#]: adjusted for ICS dose, age and sex. ICS dose, age and sex were calculated in the same model so that they compensate for each other. [¶]: comorbidities during the follow-up period: comorbidities were calculated one at a time in a model with ICS dose, age and sex, such that the comorbidities are independent of each other. The rate of comorbidities was compared between the patients without the disease (reference) and the patients with the disease.

High-dose ICS use was statistically significantly associated with a doubling of prescriptions of drugs for osteoporosis and a 52% increase in any osteoporosis-related event, while low-dose ICS use had a small but significantly higher risk of osteoporosis-related events. These findings are in accordance with the meta-analysis of RCTs and observational studies conducted by Loke *et al.* [13]. However, our findings are not in line with data from some large RCTs, such as the TORCH study [27] and the KRONOS trial [17], where no difference was observed in terms of change in bone mineral density between patients treated with an ICS combination compared with those treated with LAMA plus LABA. The reasons for such a difference may be attributed to the: 1) the follow-up duration was much longer in our study compared with those RCTs and 2) the RCTs were conducted in a highly selected population [28], unlike our study.

The risk of fractures and osteoporosis was higher in COPD patients who had concomitant asthma. To the best of our knowledge, this association has not been previously studied; however, published evidence suggests that patients with both COPD and asthma are more vulnerable in terms of exacerbations, quality of life and symptoms compared with those with neither disease [29–32]. In a recent analysis of the present study, we also found that COPD patients with concomitant asthma had a higher risk of pneumonia [6]. Both these findings are somewhat problematic as treatment with ICS is generally recommended in patients who have both COPD and asthma [33]. Additional risk factors for fractures and osteoporosis include comorbid conditions other than asthma and female sex. The prevalence of cardiovascular diseases was twice as high in the COPD groups as the control group. This may have consequences such as higher level of exercise limitation; low physical activity in the COPD group is a well-known risk factor for osteoporosis [34]. Depression is associated with physical inactivity [35], and it is therefore possible that this at least partly explains the association between depression and osteoporosis. Previously published studies support the finding that the risk of osteoporosis and/or fractures is higher in females than in males [12, 22, 36, 37]. The results regarding diabetes were somewhat paradoxical, with a positive association to fractures but a negative association to osteoporosis diagnosis and treatment. This indicates that osteoporosis is underdiagnosed and undertreated in patients with diabetes.

The present study has several important strengths. The real-world study design and the large sample size of high-quality national registry data from primary care settings adequately reflect the general population and clinical practice in Sweden. Additionally, measurement of the comprehensive range of outcomes over the extended assessment period (2000–2014) generated robust data to assess the differences between COPD and non-COPD patients. Further strengths of the study are the inclusion of a reference population, presence of other comorbidities, including asthma, and ICS use stratified by dose.

Nevertheless, this study also has certain limitations. A major problem is that we lack data on variables that are potential effect modifiers such as smoking, body mass index and physical activity. The retrospective study design introduces the potential for bias and confounding due to variables that may not have been accounted for in our analysis. Although all patients had physician-diagnosed COPD, the accuracy of COPD diagnoses and the severity of disease could not be verified, as spirometry data were not available in many patients. This study was conducted only in Swedish patients; it is therefore uncertain whether these findings can be extrapolated to a more diverse group of patients and to other healthcare systems. Furthermore, the reference population was identified from primary care centres rather than from healthy individuals in the general population. Also, in the high-dose ICS group, the number of patients treated with osteoporosis drugs was twice that of patients who had a diagnosis of osteoporosis, suggesting that all osteoporosis diagnoses had not been captured in the study. Finally, patients who had used OCS more than once for any reason (including, e.g. exacerbations) were excluded. Had we also included these patients, the difference in osteoporosis-related events between the COPD patient and reference groups would probably have been even larger.

Clinical implications

This study shows that patients with COPD are more susceptible to bone fractures and osteoporosis than those of the same age and sex without COPD. The treatment of COPD patients, especially with high-dose ICS, is associated with a higher risk of bone fractures and osteoporosis-related events. It is therefore important to screen COPD patients for osteoporosis and identify patients at high risk of fracture. The indication for osteoporosis screening is high in COPD patients with comorbidities such as asthma, cardiovascular disease and depression as these patients have an increased risk of fractures and osteoporosis. In some patients, discontinuation of ICS might be warranted and there are studies showing that it is often possible to discontinue ICS treatment in patients who are receiving LAMA plus LABA therapy with ICS [38, 39].

Conclusions

We conclude that COPD is an independent risk factor for osteoporosis and fractures. The use of high-dose ICS in COPD patients was associated with a higher risk of fracture and osteoporosis compared with

low-dose ICS. This finding further strengthens the recommendation to screen COPD patients for osteoporosis and to prescribe ICS on strict indication in patients with COPD.

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Author contributions: All authors participated equally in the study conception, design, statistical analysis planning, analysis and interpretation of the data, and have reviewed and approved the manuscript.

Conflict of interest: C. Janson reports personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis and Teva, outside the submitted work. K. Lisspers reports personal fees from AstraZeneca, Novartis, Boehringer Ingelheim, GlaxoSmithKline and Chiesi, outside the submitted work. B. Ställberg reports personal fees from AstraZeneca, Novartis, Boehringer Ingelheim, GlaxoSmithKline, Meda, Teva and Chiesi, outside the submitted work. G. Johansson has nothing to disclose. F.S. Gutzwiller is an employee of Novartis Pharma AG. K. Mezzi is an employee of Novartis Pharma AG. L. Mindeholm is a consultant to Novartis, and shareholder of Novartis, Alcon and Novo-Nordisk. B.K. Bjerregaard is an employee of IQVIA and received remuneration in relation to statistical analyses. L. Jörgensen is an employee of IQVIA. K. Larsson has, during the last 5 years, on one or more occasion served in an advisory board, served as a speaker and/or participated in education activities arranged by AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Takeda, Novartis, Chiesi, Orion and Teva.

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