

**Unintended Effects
of Inhaled Corticosteroids:
Disease or Drugs?**

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Unintended Effects of Inhaled Corticosteroids: Disease or Drugs?

Onbedoelde effecten van inhalatiecorticosteroiden,
ziekte of geneesmiddelen?

(met een samenvatting in het Nederlands)

Proefschrift

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Contents

Chapter 1	Introduction and scope	7
Chapter 2.1	Reanalysis of two studies with contrasting results on the association between statin use and fracture risk: the General Practice Research Database	19
Chapter 2.2	Use of beta-blockers and the risk of hip/femur fracture in the United Kingdom and the Netherlands	35
Chapter 3.1	Fracture risk with intermittent high-dose oral corticosteroid therapy	51
Chapter 3.2	Severity of obstructive airway disease and risk of osteoporotic fracture	63
Chapter 3.3	Use of inhaled and oral corticosteroids, severity of inflammatory disease and risk of hip/femur fracture: a population-based case-control study	77
Chapter 3.4	Use of beta-2 agonists and risk of hip/femur fracture: a population-based case-control study	91
Chapter 4.1	Evidence for no association between use of beta-2-agonists and risk of acute myocardial infarction in patients with hypertension	105
Chapter 4.2	Use of inhaled corticosteroids and the risk of non-fatal acute myocardial infarction	119
Chapter 5	Discussion	131
Appendices		
	Summary	152
	Samenvatting	157
	Acknowledgements	163
	List of publications	165
	Curriculum vitae	167

Chapter 1

Introduction and Scope

The global burden of respiratory disease

It has been estimated that 1.2-6.3% of the global population suffer from asthma, and 9-10% of adults aged ≥ 40 suffer from Chronic Obstructive Pulmonary Disease (COPD).¹⁻⁵ In 2002, obstructive airway diseases (OAD, asthma and COPD) accounted for an estimated 6.5% of the total deaths in the world. A working definition of asthma is “a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role.” The chronic inflammation results in increased airway hyperresponsiveness that, in turn, leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. These episodes occur at night or in the early morning and are usually associated with widespread but variable airflow obstruction which can be often reversible, either spontaneously or with treatment.⁶ A working definition of COPD is “a disease state characterised by airflow limitation that is not fully reversible”. This limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.⁷

Current pharmacological treatments for OAD include the use of bronchodilators (mainly beta-2 agonists, inhaled anticholinergics and, to a lesser extent, xanthine derivatives), inhaled corticosteroids (ICS), oral corticosteroids (OCs), leukotriene receptor antagonists and acetylcystein.⁸ Although the effectiveness of ICS has been established in the treatment of asthma, its beneficial effects on several outcomes (Forced Expiratory Volume in one second (FEV1), exacerbations, quality of life, mortality) after three years of treatment in patients with COPD is controversial.⁹⁻¹⁴

The burden of osteoporosis

Bone loss and fracture risk are considered as serious potential side effects of drug treatment. Osteoporosis is a disease that is characterised by a decreased bone mineral density (BMD) and a disturbed microarchitecture, resulting in fragile bones that are more likely to break. Osteoporosis can progress painlessly until a bone fracture occurs. Fragility fractures usually occur in the hip, spine, lower arm and wrist. Of these, a hip fracture usually has the greatest impact on someone's life: it has been estimated that 20-24% die in the year after a hip fracture and 33% become totally dependent or need residential care.^{15,16} As of 1990, the global burden of hip fractures had been estimated at an annual incidence rate of 0.95/1000.^{17a} Important risk factors for osteoporosis and fragility fracture include low BMD, female gender, advanced age, low body weight, patient history of fracture, family history of fracture, rheumatoid arthritis,

menopausal or oestrogen deficiency, an inactive lifestyle, severe immobility, Caucasian or Asian racial origin, and/or recent exposure to OCs.^{17b}

A possible association between use of ICS and risk of osteoporotic fracture

The first ICS in metered dose aerosols were introduced in the United Kingdom (UK) in 1972. In patients with severe asthma, inhaled beclomethasone dipropionate appeared to be an effective alternative to long-term treatment with systemic glucocorticoids, avoiding side effects related to adrenal suppression. Clinical improvements included substantial weight loss, catch up in growth suppression in children and disappearance of Cushingoid symptoms.^{18,19} Several “success stories”, such as the following case report, illustrate the revolution in the treatment of respiratory disease:

“This patient was born in August 1969 and his asthma began at six months. When first seen at 21 months, he had already been in hospital five times with acute asthma, and was admitted thrice more within the next few months, once requiring intensive care. No possible clues to the cause were found, but a nasal smear was loaded with eosinophils. Finally, he was established on 20 units corticotrophin twice a week, but after six months was still liable to sudden and serious attacks requiring hospitalisation and large doses of oral steroids. He became grotesquely Cushingoid in appearance but at the age of 30 months there seemed no alternative. His mother, however, also asthmatic, pointed out that he could take DSCG (disodiumcromoglycate) effectively, so it was decided to try aerosol therapy (i.e. inhaled beclomethasone dipropionate in a metered dose aerosol, FV). For the past nine months, thanks to the boy’s intelligence and mother’s cooperation, he has been well controlled on the aerosol, with disappearance of the Cushingoid features. In the beginning, oral steroids were required on occasion but have not been needed for the past six months.”¹⁸

In the mid-80s, ICS were widely prescribed in dosages up to 400–600 µg beclomethasone equivalent daily for the control of moderate asthma,²⁰ usually when patients had not responded to treatment with beta-2 agonists in combination with cromones or theophylline.^{21,22} Nevertheless, in the late 90s, there was widespread recognition that ICS improved airway hyperresponsiveness, symptoms of asthma and lung function, presumably by reduction of airway inflammation. These improvements in symptoms extended to patients with mild symptoms. Subsequently, ICS became generally accepted as the mainstay of asthma treatment.²³ Between 1990 and 1997, their use almost doubled in the UK and the Netherlands, whereas the use of OCs and bronchodilators substantially decreased.²⁴ The increased use of ICS was accompanied by a trend towards prescribing higher daily dosages, the so-called “start high-

go low” approach: in patients with mild to moderate asthma, a starting dose of 800-1,000 µg beclomethasone should be lowered as soon as asthma control was reached.²⁵⁻²⁷ Furthermore, during this period, it was suggested that ICS could improve airway obstruction²⁸ and could therefore also be prescribed to patients with COPD.²⁷ In 1998, an estimated 60% of the patients with COPD received ICS treatment in the Netherlands.²⁹

In 2000, it was even suggested that a better control of asthma among continuous users of ICS might prevent death from asthma.³¹ However, there was also a growing interest in unintended adverse events. Although higher dosages of ICS (>1,600 µg beclomethasone/day) had already been associated with adrenal suppression one year after introduction in the UK,³²⁻³⁴ it was not considered of great importance, probably because ICS had dramatically improved the benefit-risk ratio compared with long-term oral OC treatment.^{20,35} Nevertheless, the start high-go low” approach and the introduction of possible alternative treatments, such as long-acting beta-2 agonists and leukotriene-receptor antagonists, resulted in an awareness of potential harmful side-effects of high dose ICS use, similar to those of OCs, including bruising, growth suppression, cataract and changes in bone metabolism.³⁶

The possible association between use of ICS and osteoporotic fracture was fuelled by two epidemiological studies that reported that the risk of fracture and low BMD was increased in patients taking ICS, particularly at higher doses.^{30,37} Figure 1.1 shows the main findings of a prospective cohort study, in which premenopausal women with asthma were followed for three years. Israel and co-workers demonstrated a negative correlation between the average daily dose of inhaled triamcinolone acetonide and BMD at the total hip region. Each additional 100 µg puff (equivalent to 50 µg inhaled beclomethasone) was associated with a decline in bone density of 0.00044 g per square centimetre per year.³⁰ Figure 1.2 shows the pivotal findings of a retrospective case-control study that has been conducted in the UK General Practice Research Database (GPRD) by Hubbard and colleagues. A dose-related association between ICS use and risk of hip fracture was demonstrated, with an estimated 1.9-fold increased risk of hip fracture among users of >1,600 µg beclomethasone equivalents (eq.)/year.³⁷

The aetiology of the increased risks of osteoporosis and fracture in patients using ICS has been controversial. Based on findings of decreased BMD with increasing doses of ICS, Israel et

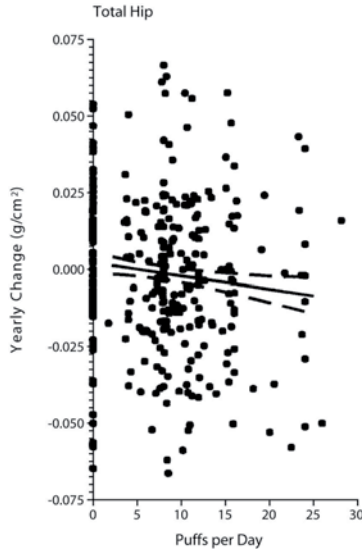


Figure 1.1 Change in bone density per year in relation to the average number of daily puffs of inhaled triamcinolone acetonide from diary cards during the intervals between visits. The rate of decline in bone density was 0.00044 g per square centimetre per year for each additional daily puff of inhaled triamcinolone acetonide ($P=0.01$). The solid line represents the mean yearly change in bone density. The dashed lines indicate the 95 percent confidence interval for the mean.³⁰ Copyright © 2001 Massachusetts Medical Society. All rights reserved.

al have concluded that ICS lead to a dose-related loss of bone at the hip in premenopausal women.³⁰ In a letter to the editor following this publication, van Staa and co-workers pointed that their large cohort study found a dose-related increase in the risk of fracture not only among users of ICS, but also among those who had used bronchodilators.³⁸ They suggested that the excess risk reported by Israel and colleagues was more likely to be related to the presence of underlying respiratory disease than to its treatment. In another letter, van Staa and colleagues argued that it seemed a flaw to relate Hubbard's dose-response association between ICS use and the risk of hip fracture to the drug, without accounting for correlating indicators of the severity of the underlying disease.^{37,39} A further understanding of the relative contributions of ICS and underlying disease to the increased risks of fracture and osteoporosis is clinically important. If these excess risks of osteoporosis and fracture are primarily related to the systemic absorption of ICS, then replacement of ICS treatment may be considered, especially in high-risk patients. In contrast, substitution of ICS treatment with another treatment would not be an option if the excess risks of osteoporosis and fracture were primarily related to the underlying disease.

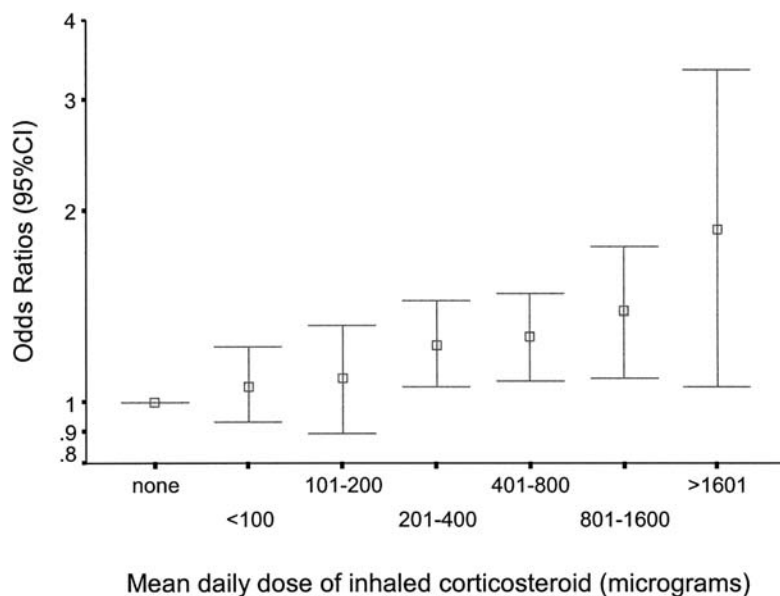


Figure 1.2 Dose-response relationship between mean daily dose of ICS and hip fracture (adjusted for exposure to oral corticosteroids). The figure has been adapted from the American Journal of Respiratory and Critical Care Medicine,³⁷ the official journal of the American Thoracic Society. Copyright © 2006 American Thoracic Society.

Fracture risk during ICS treatment: caused by the drug?

ICS are administered locally in dosages that are several times lower compared to OCs. It has been demonstrated that the areas under the curve of beclomethasone dipropionate and its equipotent, active metabolites were similar after oral or inhaled administration of 1 mg.^{40,41} The increased plasma cortisol levels that have been reported in users of ICS support this biological mechanism.⁴² Its plausibility is extended by the possible adverse events that have been described for the use of ICS in adults.

Osteoporotic fracture should be considered as a severe side effect of systemic corticosteroid treatment. Although early reports of the tendency of patients with excess systemic corticosteroid use to develop bone fractures were described by Cushing in 1932,⁴³ the first reliable estimates for the risk of hip, spine, and wrist fractures in OC users were only published six years ago. It was shown that the risk of fracture increases very rapidly after starting OC use and that it declines quite rapidly after discontinuation. There was no threshold dose at which OCs can be considered to be clearly safe.^{44,45}

Given the dose-dependent risk of fracture in users of OCs, a dose-response association between ICS use and risk of fracture was hypothesised.³⁷

Fracture risk during ICS treatment: confounded by the severity of the respiratory disease?

Confounding by the severity of the underlying respiratory disease is a well-recognised problem in observational research that evaluates dose-response associations with respiratory medications and health outcomes like mortality. In 1968, an association between the use of a more potent formulation of the beta-2 agonist isoproterenol and increases in asthma mortality in the UK, Australia and New Zealand was reported. As this increase in mortality was not observed in countries where the potent formulation was unavailable, the first concerns about the safety of beta-2 agonists were raised.⁴⁶ More than one decade later, there was a dramatic increase in asthma mortality in New Zealand. Then, a 1989 epidemiological study associated the elevated death rate to the introduction of the inhaled beta-2 agonist fenoterol.⁴⁷ The core of subsequent debate pivoted on whether heavy use of beta-2 agonists was a cause of increased mortality or whether it was a marker of very severe asthma, with an association between exposure and death being coincidental.⁴⁸⁻⁵¹ After more than six years of this dispute, a round table discussion was organised, with a result that in 1997, most researchers had agreed that confounding by disease severity -and not a causal relationship- was reflected by the increasing risks of mortality observed with increasing doses of bronchodilators.⁵²

Patients with more severe OAD are usually treated with higher dosages of ICS. In addition to ICS use, the severity of the underlying respiratory disease has been associated with a decreased BMD, regardless of ICS or OC exposure.^{53,54} An analysis of the third National Health and Nutrition Examination Survey (NHANES) revealed that the risk of osteoporosis among males and females was inversely correlated with the degree of their airway obstruction. Adjustment for ICS, OCs or bronchodilators did not change these results.⁵⁴ A cross-sectional study in a general-practice setting among British females aged 45-76 years also showed an inverse relationship between forced expiratory volume in one second and BMD at the hip, which remained similar after exclusion of patients who had a history of respiratory disease.⁵³ Smoking, hypercapnia and chronic inflammation may correlate with the severity of OAD and have therefore been proposed as explanations for the observed decline in BMD.⁵⁵⁻⁵⁸

Scope

The overall aim of this thesis is to examine the association between the use of ICS and risk of fracture. Respiratory disease severity is a potential confounding factor that is difficult to measure in health care databases.⁵⁹ To deal with this challenge, the hypothesis of confounding by the severity of respiratory disease and its competing hypotheses (i.e. of a causal relationship between ICS use and risk of fracture.) will be evaluated. These hypotheses will be extended with alternative hypotheses in order to assess the plausibility in the light of biological knowledge and other evidence.^{60,61}

In **Chapter 2**, two examples of this approach are shown in the evaluation of two previously published observational studies. Pivotal results of these epidemiological studies have demonstrated that use of statins (cholesterol-lowering agents) or beta-blockers (blood-pressure lowering agents) may protect against risk of fracture. Given the unexpected magnitude of the reported fracture risk reductions, we hypothesised that the previously published results were distorted. The analyses were repeated after specific exposure analyses were designed in order to test whether the observed risk estimates were in line with the current knowledge of the underlying biological mechanisms.

In **Chapter 3**, the hypothesis of confounding by the severity of the respiratory disease was evaluated. In addition, the competing hypotheses of an increased risk of fracture due to systemic absorption of ICS or beta-2 agonists was tested, using statistical adjustments for indicators of the severity of the respiratory disease.

In **Chapter 4**, the alternative hypothesis that systemic absorption of respiratory medications may decrease (ICS) or increase (beta-2 agonists) the risk of non-fatal acute myocardial infarction (MI) was tested. In order to support the assumption that plasma levels of ICS/beta-2 agonists were not high enough to affect bone remodelling, we hypothesised that this would be similar for other health outcomes, such as non-fatal acute MI.

Data sources used in this thesis

In this thesis, we used two different data sources (Table 1): the UK GPRD (www.gprd.com) and the Dutch PHARMO Record Linkage System (PHARMO RLS, www.pharmo.nl). In the UK, general practitioners (GPs) act as gatekeepers for the health care system, as they are responsible for primary health care and specialist referrals.^{62,63}

Table 1.1 Overview of data sources and datasets that have been used in several chapters (values) in this thesis.

Exposure of interest	GPRD			PHARMO RLS	
	Cohort (OC users) 1991-1998	Case-control dataset (fractures) 1987-1999	Case-control dataset (fractures) 1987-2002	Case-control dataset (hip/femur fractures) 1991-2002	Cohort (antihyper- tensive drug users) 1991-2003
ICS		3.2		3.3	4.2
Beta-2 agonists		3.2		3.4	4.1
OCs	3.1			3.3	
Statins			2.1		
Beta-blockers		2.2		2.2	

ICS: inhaled corticosteroids; OCs: oral corticosteroids.

In 2006, the GPRD contained computerised medical records of almost 500 practices, including 8 million people. The data stored in GPRD include demographic information, prescription details, clinical events, clinical laboratory data, preventive care provided, specialist referrals, hospital admissions and hospital discharge summaries. Several independent validation studies have confirmed the high level of completeness and validity, including data for respiratory disease and non-vertebral fractures.⁶⁴⁻⁶⁷

The PHARMO RLS includes the demographic details and complete medication histories of over two million community-dwelling residents in more than 50 population-defined areas in the Netherlands from 1986 onwards, further linked to hospital admission records as well as several other health registries, including pathology, clinical laboratory findings and general practitioner data.⁶⁸ Since nearly all patients in the Netherlands are registered with a single community pharmacy, independently of prescriber, pharmacy records are virtually complete with regard to prescription drugs.^{69,70} Validation studies have confirmed the high level of completeness and validity, including data for respiratory medications and hip fractures.^{24,71,72}

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Chapter 2.1

Reanalysis of Two Studies with Contrasting Results on the Association Between Statin Use and Fracture Risk: the General Practice Research Database

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Summary

Background. Two recent case-control studies by Meier et al and van Staa et al used the UK General Practice Research Database (GPRD) to examine the association between the use of statins and the risk of fractures, with different results. The objective of the present study was to examine methodological explanations for the discrepant results.

Methods. We created two datasets, which mimicked the previous study designs: a “selected population” (SP) case-control dataset, with fracture cases matched to controls nested within a selected cohort (Meier et al), and an “entire population” (EP) case-control dataset, with both cases and controls sampled from the total GPRD population (van Staa et al). Cases and controls were matched by gender, age (year of birth or five year age bands), and general practice.

Results. The study included 131,855 fracture cases. The crude odds ratio (OR) for hip fracture in statin users was 0.37 [95% CI 0.27-0.52] in the SP and 0.54 [95% CI 0.39-0.74] in the EP dataset. This difference was reduced when matching by year of birth, rather than by 5 year age bands: crude ORs were 0.58 [95% CI 0.43-0.79] and 0.61 [95% CI 0.44-0.88], respectively. In the SP dataset, 37% of the cases could be matched by year of birth, while this was achieved for 99% in the EP dataset. The exposure time-window, the selection of confounders, and exclusion of high-risk patients also influenced results.

Conclusion. Residual confounding by a matching variable and different definitions of the exposure time window explained differences in results. In case-control studies of drug use and fracture risk, broad matching criteria for age should be avoided and the selection of the time-window for exposure should be carefully considered.

Introduction

Following the finding that statins increase bone formation in rodents,¹ two studies independently evaluated the association between the risk of fracture and use of statins in humans.²⁻⁴ Although in both studies medical records from the UK General Practice Research Database (GPRD) were used, different results were obtained. Meier and co-workers reported a statistically significant ($P < 0.001$) odds ratio (OR) of 0.12 [95% CI 0.04-0.41] for hip fracture in current statin users compared with non-users, while van Staa and co-workers found an OR of 0.59 [95% CI 0.31-1.13].

In the subsequent discussion, Meier proposed that inclusion of patients at high risk of fractures might have led to biased results in the study by van Staa et al.⁵ In an editorial, Hennesy and Strom suggested that the inclusion of patients who sustained “unspecified fractures”, the use of different coding dictionaries and different time-window definitions for statin exposure might explain the different results.⁶ Van Staa argued that varying definitions of follow-up between users and non-users could have created an imbalance in the matching of fracture cases in the study by Meier et al.^{3,7} None of these hypotheses have been formally tested. Furthermore, randomised clinical trials (RCTs) have provided little evidence for statins as anti-osteoporotic agents (Figure 2.1.1).⁸⁻¹¹ The objective of this study was to examine whether different matching procedures, time-window definitions, and exclusion criteria might explain the discrepant results of the two case-control studies by Meier et al and van Staa et al.^{2,3} Table 2.1.1 lists the major differences between both study designs, including those that this paper will evaluate as the reason for the different results.

Methods

We replicated the study design of Meier et al [referred to as the “selected population” (SP) case-control dataset] and the study design of van Staa et al [“entire population” (EP) case-control dataset] in the GPRD with data collected from 1 January 1987 through 30 April 2002. The complete dataset included all permanently registered patients aged 50 years or older.

Table 2.1.1 Major differences between two original case-control studies in which the association between fracture risk and statin use was evaluated.^{2,3}

Characteristic	Original “SP” case-control study ²	Original “EP” case-control study ³	Difference evaluated in current study?
Study population	Users of lipid lowering drugs, patients with a diagnosis of hyperlipidemia and 50,000 untreated patients who were enrolled between the late 80s and September 1998.	All subjects enrolled between January 1987 and July 1999.	No, the current study was evaluated in the GPRD with data from January 1987 to April 2002
Study design	Cases and controls were selected from a subset of the study population	Cases and controls were selected from the complete study population	No, information on the selection of the GPRD subset was not available
Age (years)	50 through 89 at start of follow-up.	50 and older at the index date.	Yes
Study outcome	Fractures of the femur/hip, humerus, hand, wrist or lower arm, vertebrae, clavicle, foot or malleolus or an unspecified location	Fractures of the vertebrae, clavicle, humerus, radius/ulna, carpus, hip, ankle, or foot	No, the outcome studied comprised the fracture types from the original “selected population” case-control study.
Exclusion criteria at baseline	History of osteoporosis, osteomalacia, alcoholism, cancer excluding non-melanoma skin cancer and previous use of bisphosphonates.	None.	Yes
Definition current statin use	At least one statin prescription, but no other lipid lowering drugs in the 30 days before the index date.	At least one statin prescription in the six months before the index date, regardless of other lipid lowering drugs.	Yes
Matching variables	Age, gender, general practice and duration of follow-up.	Age, gender and general practice.	Yes
Disease coding	ICD-8 cross-mapping	ICD-9 cross-mapping	No, ICD-9 coding dictionary was used
Variables included in multivariate analysis	Exposure to HRT, oral corticosteroids, smoking, BMI, and the number of GP visits (“limited adjusted model”).	All potential confounders in the Methods section of this paper (“fully adjusted model”) including anemia and depression, but without a history of diabetes, rheumatoid arthritis, falls, smoking, NSAID, bronchodilator and beta-blocker use.	Yes, adjustment with the “fully adjusted model” and the “limited adjusted model” was evaluated.

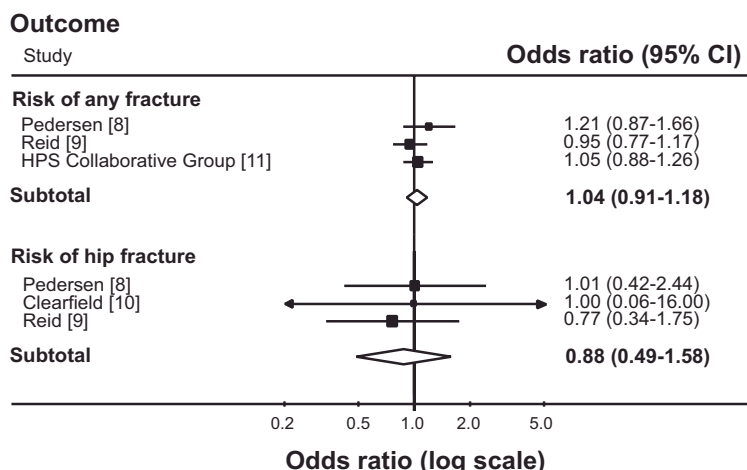


Figure 2.1.1 Effects of statins on risk of fracture in randomised controlled clinical trials.

SP case-control dataset

The SP case-control dataset was created in three defined cohorts of patients.² The first cohort included all patients who received at least one prescription for a statin (i.e. atorvastatin, cerivastatin, fluvastatin, pravastatin, or simvastatin), a fibrate (i.e. bezafibrate, ciprofibrate, clofibrate, fenofibrate, or gemfibrozil), or a lipid-lowering drug other than statins or fibrates (i.e. colestipol-hydrochloride, cholestyramine, acipimox, or nicotinic acid). The second cohort consisted of all people with a diagnosis of hyperlipidaemia and the third cohort consisted of a random sample of 250,000 people who received neither a diagnosis of hyperlipidaemia nor a prescription for a lipid-lowering drug at any time. These patient numbers are proportionally similar to those analysed by Meier et al.² Start of data collection was defined as the date of enrolment of a patient in a practice or the date of enrolment of a practice in GPRD, whichever came later. The start of follow-up for this study was defined as the date of the first prescription of a lipid-lowering drug (cohort one) or as the start of data collection (cohorts two and three).

Within these cohorts, all patients with a first occurrence of a fracture were identified. The fractures were restricted to those of the femur/hip, humerus, hand, wrist, or lower arm, vertebrae, clavicle, foot, or malleolus or an unspecified location, similar to those selected by Meier et al.² The date of the fracture was taken as the index date. From the three cohorts, up to six control patients were randomly selected for each case. Cases and controls could be selected from different cohorts. They were matched by year of

birth, sex, practice, and the year of start of follow-up using the incidence density sampling technique. Controls had to be alive and enrolled in GPRD at the index date. If no controls of similar age could be found, the age band used for matching was expanded stepwise up to a maximum of five years.² If no control within the five year age band could be identified, the case was matched to a control with similar matching parameters except for the practice criterion. Control patients had the same index date as their matched case.

EP case-control dataset

The EP case-control dataset was created in the total GPRD population of patients aged 50 years or older, similar to the methodology used by van Staa and co-workers.^{3,4} Cases were permanently registered patients with a first-ever fracture after the start of data collection. Each case was matched to one control patient (patients without a history of any type of fracture) by year of birth, calendar time, sex, and general practice using the incidence sampling technique.

Exposure assessment

Users of lipid-lowering agents were classified according to single or mixed use before the index date of statins, fibrates, or other lipid-lowering drugs, according to the classification in the original SP analysis.² As the time-window for exposure to lipid-lowering drugs was defined differently in the two original studies, two definitions were used. In the first definition (similar to that used by Meier et al), current users were patients who were prescribed a lipid-lowering drug in the 30 days or less before the index date. The second exposure definition (similar to that used by van Staa and co-workers) defined current users as patients who were prescribed a lipid-lowering drug in the six months or less before the index date. Exposure duration was assessed by counting the number of statin prescriptions, as used in the original SP study design.² Time since first statin use was determined by calculating the period between index date and first prescription.

Statistical analysis

Crude ORs of fracture in statin users compared with never users and 95% confidence intervals (CI) were estimated using conditional logistic regression. A history of diabetes mellitus, rheumatoid arthritis, congestive heart failure, seizures, thalassaemia, sickle cell disease, pernicious anaemia, dementia, psychotic disorder, stroke, chronic obstructive pulmonary disease and a history of hyperthyroidism or falls one year before the index date were considered as

potential confounding variables. Prescribing in the six months prior to index date for anticonvulsants, methotrexate, hormone replacement therapy (HRT), thiazide diuretics, beta-blockers, anxiolytics/hypnotics, antipsychotics, antidepressants, anti-Parkinson drugs, systemic and inhaled corticosteroids, bronchodilators, and a minimum of three prescriptions of non-steroidal antiinflammatory drugs (NSAIDs) were also included in the regression analysis. The last recorded smoking status and body mass index (BMI) before the index date, were also included (some practices do not enter these data since it is not part of required data collection). Adjustment for these variables is referred to as the “fully adjusted model”. In order to replicate the adjustments in the original analysis by Meier et al,² the number of general practitioner (GP) visits before the index date was also calculated. Final adjusted models were fitted using backward elimination. The Mantel-Haenszel estimator of combined ORs of RCTs in Figure 2.1.1 was calculated according to the method described by Hauck.¹² Spline regression lines were calculated using the GPLOT procedure of SAS version 8.2 (SAS Institute Inc., Cary, NC, USA).

Results

Totally 131,855 patients sustained one or more fractures, and 126,028 patients received one or more prescriptions for lipid-lowering drugs in the GPRD population of patients aged 50 years or older. Table 2.1.2 shows baseline characteristics in the two case-control datasets. In the SP case-control dataset, only 37% of the cases had been matched to controls by year of birth, while this was achieved for 99% of patients in the EP case-control dataset.

The risks of fracture among those who had received one or more statin prescriptions in the six months before were generally lower with the SP case-control dataset, compared with the EP case-control dataset (Table 2.1.3). This was particularly obvious for patients who sustained a hip fracture, yielding an OR of 0.48 [95% CI 0.36-0.64] in the SP dataset, and 0.60 [95% CI 0.46-0.78] in the EP dataset (when adjusting for the variables originally used by Meier et al). Adjustment with a larger set of potential confounders reduced the magnitude of effect (OR for risk of hip fracture of 0.60 [95% CI 0.45-0.81] in the SP dataset and 0.72 [95% CI 0.54-0.95] in the EP dataset).

The use of shorter time-windows for measuring current statin use reduced the ORs for fracture. The fully adjusted OR for hip fracture was 0.49 [95% CI 0.24-1.00] in the EP case-control

Table 2.1.2 Characteristics of cases and controls in the SP and the EP case-control datasets.

Characteristic	"SP" case-control design				"EP" case-control design			
	Cases		Controls		Cases		Controls	
	n=17,948	(%)	n=95,468	(%)	OR (95% CI)	n=131,838	(%)	OR (95% CI)
Mean age years	72.0		71.1			71.6		
Degree of matching								
By same year of birth			35,650	37%			130,291	99%
Control 1-5 years older			26,970	28%			541	0%
Control 1-5 years younger			32,848	34%			1,033	1%
Number of women	13,726	76%	72,274	76%		98,762	75%	
Mean duration of follow-up years	3.5		3.5			4.0		
BMI								
<20	689	4%	2,730	3%	1.21 (1.10-1.32)	5,610	4%	1.21 (1.16-1.26)
20-25	4,228	24%	21,072	22%	1.00	30,330	23%	1.00
25-29.9	3,823	21%	20,784	22%	0.92 (0.88-0.97)	24,668	19%	0.90 (0.88-0.92)
≥ 30	1,544	9%	8,943	9%	0.86 (0.81-0.92)	9,701	7%	0.84 (0.81-0.86)
Unknown	7,664	43%	41,939	44%	0.90 (0.85-0.94)	61,529	47%	0.89 (0.87-0.91)
Smoking status								
Current smoker	2,019	11%	10,091	11%	1.08 (1.02-1.14)	15,333	12%	1.10 (1.07-1.13)
Ex smoker	1,272	7%	6,111	6%	1.12 (1.05-1.20)	7,763	6%	1.09 (1.05-1.13)
Non-smoker	8,344	46%	43,699	46%	1.00	58,766	45%	1.00
Unknown	6,313	35%	35,567	37%	0.91 (0.87-0.95)	49,976	38%	0.91 (0.89-0.93)
Diseases before index date								
Heart failure	781	4%	3,157	3%	1.23 (1.13-1.34)	5,986	5%	1.32 (1.27-1.37)
Stroke	473	3%	1,711	2%	1.41 (1.27-1.57)	3,563	3%	1.50 (1.43-1.58)
Diabetes mellitus	306	2%	1,613	2%	1.00 (0.88-1.13)	2,330	2%	0.99 (0.94-1.05)
Drug use 182 days before index date								
Thiazide diuretics	2,498	14%	14,121	15%	0.92 (0.88-0.96)	16,445	12%	0.93 (0.91-0.95)
Systemic corticosteroids	1,202	7%	4,109	4%	1.59 (1.48-1.70)	8,231	6%	1.63 (1.57-1.69)
HRT	610	3%	4,338	5%	0.74 (0.67-0.81)	5,046	4%	0.76 (0.73-0.79)
Statin exposure only								
Never exposed to lipid-lowering drugs	14,762	82%	79,475	83%	1.00	128,572	98%	1.00
Use of statins 30 days before	951	5%	5,659	6%	0.82 (0.74-0.90)	899	1%	0.87 (0.79-0.95)
Use of statins 6 months before	1,596	9%	8,688	9%	0.92 (0.85-1.00)	1,503	1%	0.95 (0.89-1.02)
Hip fracture								
Never exposed to lipid-lowering drugs	2,470		12,223			19,366		
Use of statins 30 days before	2,217	90%	10,749	88%	1.00	19,113	99%	1.00
Use of statins 6 months before	67	3%	542	4%	0.37 (0.27-0.52)	58	0%	0.54 (0.39-0.74)
Vertebral fracture								
Never exposed to lipid-lowering drugs	122	5%	827	7%	0.47 (0.35-0.63)	111	0%	0.67 (0.52-0.85)
Use of statins 30 days before	1,077		5,665			7,606		
Use of statins 6 months before	857	80%	4,678	83%	1.00	7,393	97%	1.00
Use of statins 30 days before	55	5%	395	7%	0.62 (0.42-0.92)	47	1%	0.72 (0.49-1.06)
Use of statins 6 months before	105	10%	972	17%	0.81 (0.58-1.14)	89	1%	0.87 (0.64-1.16)

Table 2.1.3 Risk of fracture and current statin use in the original and new case-control datasets.

Exposure before	Adjusted OR (95% CI)		Adjusted OR (95% CI), according to similar confounders as used by Meier et al ^{2,a}		Adjusted OR (95% CI), according to the “fully adjusted model” described in the Methods section	
	Original dataset ^{2,b}	Original dataset ^{3,c}	Updated “SP” dataset	Updated “EP” dataset	Updated “SP” dataset	Updated “EP” dataset
Statin only						
Never exposed to lipid lowering drugs	1.00	1.00 ^d	1.00	1.00	1.00	1.00
Any fracture						
30 days prior	0.55 (0.44-0.69)		0.82 (0.74-0.91)	0.74 (0.68-0.82)	0.85 (0.77-0.94)	0.92 (0.83-1.01)
6 months prior		1.01 (0.88-1.16)	0.93 (0.85-1.01)	0.82 (0.76-0.89)	0.96 (0.88-1.04)	1.01 (0.94-1.09)
Hip fracture						
30 days prior	0.12 (0.04-0.41)		0.38 (0.27-0.53)	0.48 (0.34-0.68)	0.50 (0.36-0.68)	0.54 (0.38-0.78)
6 months prior		0.59 (0.31-1.13)	0.48 (0.36-0.64)	0.60 (0.46-0.78)	0.60 (0.45-0.81)	0.72 (0.54-0.95)
Vertebral fracture						
30 days prior	0.14 (0.02-0.88)		0.52 (0.34-0.80)	0.59 (0.38-0.92)	0.63 (0.41-0.95)	0.68 (0.44-1.05)
6 months prior		1.15 (0.62-2.14)	0.70 (0.49-1.01)	0.63 (0.45-0.89)	0.83 (0.57-1.19)	0.82 (0.59-1.14)

a Adjusted for the criteria in the original design by Meier, i.e. BMI, smoking, number of GP visits one year before, use of oral corticosteroids, and HRT six months before the index date.

b Patients with a history of osteoporosis, osteomalacia, alcoholism, cancer (excluding non-melanoma skin cancer), and bisphosphonate use prior to start of follow-up were excluded.

c Adjusted for potential confounders as listed in the Methods section, including anaemia and depression, but without a history of diabetes mellitus, rheumatoid arthritis, falls, smoking, use of bronchodilators, beta-blockers, and NSAIDs.

d Never exposed to statins.

dataset when defining exposure on the basis of statin prescribing in the one week before the index date, compared with an OR of 0.78 [95% CI 0.60-1.02] when using a time-window of two years (Figure 2.1.2). In both study designs, 60% of the case patients and 65% of the control patients who were exposed to statins in the six months before the index date, were also exposed to statins in the 30 days prior to the index date.

Table 2.1.4 shows the effects of changes in matching procedures and patient selection on the risk of hip fracture in statin users. Matching by exact year of birth, instead of using a five-year age band, decreased the differences between the two designs and moved ORs towards unity. Exclusion of patients at high risk of fracture had different effects on ORs: the magnitude of the effect in the SP dataset (adjusted OR for hip fracture of 0.44 [95% CI 0.24-0.79]) increased whereas the opposite was the case in the EP dataset (OR 0.67 [95% CI 0.46-0.98]). In the original SP case-control dataset, start of follow-up was defined differently between users and non-users of statins.

Consequently, the amount of follow-up time used to determine high-risk status differed between users and non-users of statins (means of 1.7 and 4 years, respectively). The inclusion of femur fractures with unspecified location of fracture, the exclusion

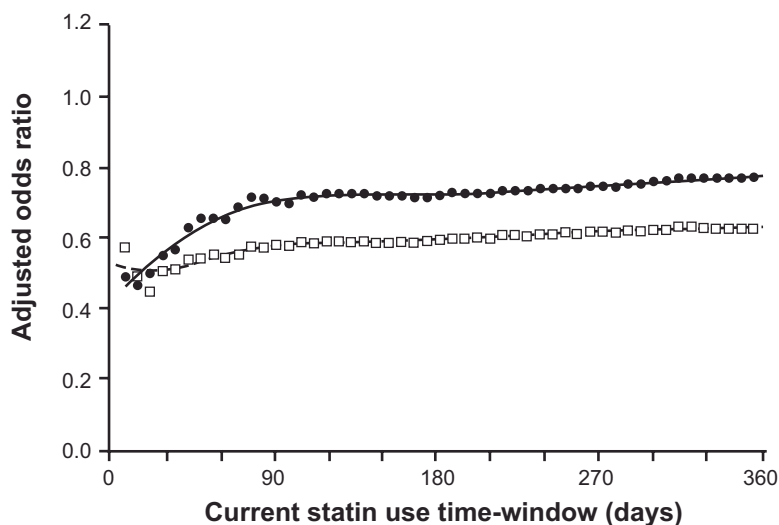


Figure 2.1.2 Spline regression plot of hip fracture risk and length (days) of the current use of statins time-window. Squares and dashed line: SP dataset. Dots and solid line: EP dataset. The current use time-window was 52 times extended stepwise by seven days, starting at seven days before the index date and ending 364 days before the index date.

Table 2.1.4 Effect of changes in matching procedures and patient selection on risk of hip fracture and statin use.

Analysis (current statin use time-window)	“SP” dataset		“EP” dataset	
	Adjusted OR (95% CI)		Adjusted OR (95% CI)	
Original analyses^{2,3}				
30 days prior	0.12	(0.04-0.41)		
6 months prior			0.59	(0.31-1.13)
Fully adjusted model				
30 days prior	0.50	(0.36-0.68)	0.54	(0.38-0.78)
6 months prior	0.60	(0.45-0.81)	0.72	(0.54-0.95)
Exclusion of high risk patients according to the original Meier analysis^a				
30 days prior	0.44	(0.24-0.79)	0.67	(0.46-0.98)
6 months prior	0.55	(0.32-0.96)	0.84	(0.62-1.13)
Matching by same year of birth instead of an up to 5 year expanding age band				
30 days prior	0.72	(0.53-0.99)	0.67	(0.47-0.97)
6 months prior	0.82	(0.63-1.05)	0.77	(0.58-1.02)
Matching by gender, age and practice but without duration of follow-up				
30 days prior	0.51	(0.39-0.68)		
6 months prior	0.60	(0.48-0.75)		

a: Patients with a history of osteoporosis, osteomalacia, alcoholism, cancer (excluding non-melanoma skin cancer), and bisphosphonate use before start of follow-up (SP dataset) or before the left censoring date (EP dataset) were excluded.

of patients who were 90 years and older, or matching by duration of follow-up in the SP case-control dataset did not substantially change results. Figure 2.1.3 shows the association between the number of statin prescriptions before the index date and the adjusted OR for hip fracture in both study designs. Among current users, the risk of hip fracture was reduced after only one statin prescription (30 days of treatment) and remained stable with increasing numbers of prescriptions.

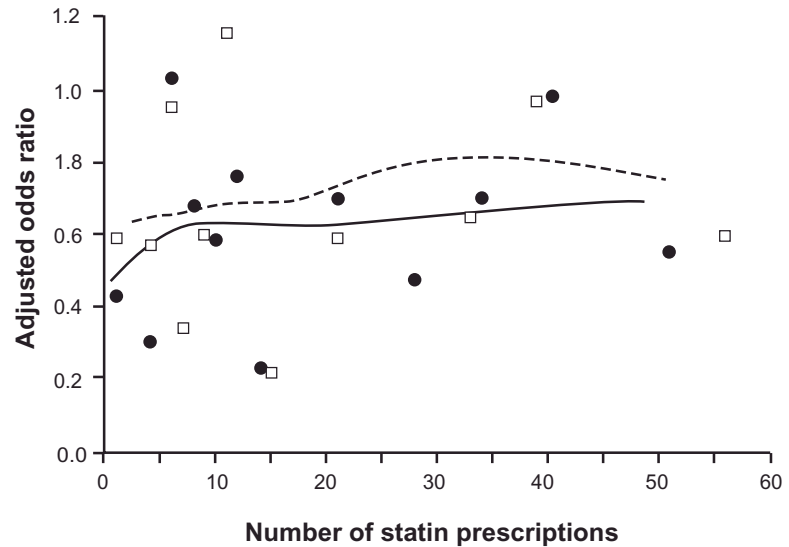


Figure 2.1.3 Spline regression plot of the number of statin prescriptions and risk of hip fracture among patients who used statins 30 days prior to index date. Squares and dashed line: EP dataset; Dots and solid line: SP dataset.

Discussion

We examined methodological reasons for the discrepant results of two previous case-control studies that examined the association between use of statins and risk of fracture in the same database.^{2,3} We found that the age-band used for matching cases and controls, the selection of potential confounders, the exclusion of high-risk patients, and different definitions for exposure time-windows led to differences in results between the SP and the EP case-control study designs.

We found that results changed substantively with the choice of the exposure time-window. The two case-control studies applied different time-windows for exposure: Meier assessed the statin prescribing in the 30 days prior to the index date, while van Staa used a six month period.^{2,3} The exposure time-window should

cover the time-period during which the drug can cause or prevent the outcome, which is related to the lag-time of effect after start of treatment and cessation of effect after treatment discontinuation. The length and timing of this exposure time-window can influence the estimates of exposure risks.^{13,14} It seems unlikely that statins' effect on the bone occur within 30 days of start of use. In vitro, statins protect bone through a mechanism similar to aminobisphosphonates.^{15,16} Two large randomised controlled clinical trials reported reductions in hip fracture risk only after 6-12 months of bisphosphonate use.^{17,18} This suggests that a longer time-window is appropriate in the evaluation of the effects of statins on the bone.

Both studies matched fracture cases to controls by age and used a matching procedure that expanded the difference in age in a stepwise manner, if no control was found. We found that the SP and EP case-control studies yielded different results when using the broader matching for age, but this difference disappeared when matching by year of birth. The SP case-control dataset based on the broad age matching criteria included hip fracture cases that were on average two years older than their matched controls in the SP dataset. In contrast, there was no difference in age between cases and controls in the EP dataset. The SP case-control study obtained controls from three selected cohorts, which included a much smaller number of patients compared with the total GPRD population used in the EP case-control study. Age is a strong risk factor for fracture risk, and residual confounding may, thus, explain part of the risk reduction observed in the SP case-control study.

In laboratory studies, Mundy et al found positive effects of statins on the expression of bone morphogenetic protein 2 (BMP-2) and bone growth.¹ Following this, several epidemiological studies were conducted. Pooling the results of these observational studies, Bauer et al reported a summary OR for hip fracture risk in statin users of 0.43 [95% CI 0.25-0.75].¹⁹ However, the pooling of the results of RCTs did not provide strong evidence for a protective effect of statins for any type of fracture (Figure 2.1.1). Our study included the largest number of statin users compared with previous research, and we were able to conduct a detailed analysis of the association between duration of statin use and risk of fracture. A decreased risk of hip fracture was found already after one statin prescription and there was no relationship between duration of statin use and size of fracture risk reduction. It seems unlikely that pharmacological effects of statins cause this reduction in risk within 30 days of statin treatment. Although Mundy reported an increased bone formation in rodents already after five weeks of simvastatin

administration,¹ this seems implausible in humans given the limited number of bone remodelling sites.

The reduced fracture risk observed in this study might, thus, be due to unknown confounders. It might be related to confounding by socio-economic status and the “healthy drug user” effect, biases that have been proposed as an explanation for different results of clinical trials and observational research in the study of HRT and coronary heart disease.²⁰⁻²³ Although few studies have examined the association between socio-economic status and hip fracture risk, a large population-based case-control study suggests that low socio-economic status is associated with increased risk of hip fracture.²⁴ In addition, in a large cohort study, lower socio-economic status appeared to be inversely associated with statin use.²⁵ Healthy user bias is likely to have occurred because long-term statin users tend to be healthier and physically more active than non-users.²⁶

Unfortunately, these hypotheses cannot be tested directly in the GPRD, as information on socio-economic status or “healthy drug users” was not available in GPRD at the time of data collection. However, as of 2006, the GPRD will be using a trusted third party to enable record linkage to other NHS datasets. Such linkage is planned for small-area deprivation indices. Inadequate adjustment for socio-economic status and healthy user bias are likely explanations for the discrepant findings between observational studies and randomised controlled trials in the study of statin use and fracture risk, but this should be examined in future studies.

The objective of this study was not to exactly replicate the results of the two studies but to test various hypotheses that could explain the discrepant results. For this purpose, we used a single dataset with similar definitions for drug exposures and diagnoses. Our study designs were not identical to those employed by Meier and van Staa, as we did not have access to all computer programs and coding dictionaries. Moreover, restoring the original datasets using the same date ranges was virtually impossible. After July 1999, several general practices have contributed additional data from the period 1987 through 1999, which were not available at the time Meier and van Staa did their analyses. Thus, our study was conducted in a larger and more recent GPRD dataset. As the use of statins has increased dramatically in recent years, the characteristics of statin users may have changed over time. Another limitation was that there was incomplete recording for BMI and smoking, as these data are not part of compulsory data collection in GPRD.

Our results have important methodological implications. Residual confounding by a matching variable may occur when a case-control study is nested within a relatively small cohort, especially when multiple matching variables are used. In case-control studies of drug use and fracture risk, broad matching criteria for age should be avoided and the selection of the time-window for exposure should be carefully considered.

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Chapter 2.2

Use of Beta-Blockers and the Risk of Hip/Femur Fracture in the United Kingdom and the Netherlands

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Summary

Background. Data from in-vivo studies have indicated a role for beta-blockers in the prevention of bone loss. Some epidemiological studies found protective effects of beta-blockers on fracture risk. However, there is limited information on the association with cumulative dose and type of beta-blockers used.

Methods. We conducted two case-control studies using data from the British General Practice Research Database (GPRD) and the Dutch PHARMO Record linkage System (RLS). Cases were patients with a first hip or femur fracture; controls were individually matched on practice/region, gender, year of birth and calendar time. Current use of beta-blockers was defined as a prescription in 90 days before the index date. We adjusted for medical conditions and drugs associated with falling or bone mineral density. Odds Ratios (ORs) and 95% confidence intervals (CI) were calculated using conditional logistic regression analysis.

Results. The study population included 22,247 cases and controls in the GPRD and 6,763 cases and 26,341 controls in the PHARMO RLS. Current use of beta-blockers was associated with a reduced risk of hip/femur fracture in both GPRD (adjusted OR 0.82 [95% CI 0.74-0.91]) and the PHARMO RLS (adjusted OR 0.87 [95% CI 0.80-0.95]) study populations. However, this reduction of risk was not associated with cumulative dose, lipophilicity or receptor selectivity of beta-blockers. The protective effect of beta-blockers was only present among patients with a history of use of other antihypertensive agents (GPRD: adjusted OR 0.72 [95% CI 0.64-0.83]; PHARMO RLS: adjusted OR 0.76 [95% CI 0.67-0.86]; but not in patients using beta-blockers only (GPRD: adjusted OR 0.97 [95% CI 0.82-1.14] PHARMO RLS: adjusted OR 1.01 [95% CI 0.90-1.14]. Also within patients with a history of use of other antihypertensive agents, no dose-response relationship with beta-blockers use was found. The effect was constant with cumulative dose and the OR was below 1.0 even among patients who just started treatment with beta-blockers.

Conclusion. As the mechanism by which beta-blockers could influence BMD is likely to need some time to exert a clinically relevant effect, all these finding suggests that the association between beta-blockers and fracture risk is not causal.

Introduction

Bone remodeling comprises a phase of resorption by osteoclasts and a phase of formation by osteoblasts. Recent studies have shown bone metabolism to be mediated through the autonomic central nervous system. Leptin, a hormone produced in fat cells to signal energy insufficiency, regulates bone remodeling by modulating osteoblast proliferation and subsequent osteoclast activation via the osteoclast differentiation factor RANK Ligand (RANKL). The antiosteogenic effect of leptin is not present in beta-2-adrenergic receptor deficient mice, which had the actual increases in bone mineral density (BMD)¹⁻⁵. Data from these in-vivo studies indicate a role for beta-blockers in the prevention of bone loss. In the early 90s, propranolol was found to increase bone formation.⁶ Some observational studies have reported that the use of beta-blockers was associated with a decreased risk of fractures⁷⁻⁹, conflicting with other studies which found no association with fractures.¹⁰⁻¹² Studies on effects of beta-blockers on sub-clinical endpoints, like BMD or biochemical markers of bone resorption, have also yielded inconsistent results.^{7, 10, 12-14}

A possible role for beta-blockers in prevention of fractures is of major clinical interest, given that fractures are a major source of morbidity, disability, hospitalisation and mortality. One of the most serious fractures resulting from accidental falls is hip fracture.¹⁵ However, there is still a lack of knowledge with respect to the effects of cumulative dose and type of beta-blockers used. Thus, the objective of this study was to assess the strength of the association between use of beta-blockers and risk of hip/femur fractures using data from two different large population-based databases in the United Kingdom (UK) and the Netherlands.

Methods

Setting

Data for this study were obtained from the UK General Practice Research Database (GPRD) and the Dutch PHARMO Record Linkage System (RLS). The GPRD (www.gprd.com) contains the computerised medical records of general practices across the UK. Approximately 6% of the total registered population of England and Wales is represented in the database and it includes a cumulative total of over five million adult patients. The age and sex distribution of patients enrolled is representative of the general English and Welsh populations. Patient details accrued in the GPRD in-

cluded demographic information, diagnoses, prescription details, preventive care provided, referrals to specialist care, hospital admissions and related major outcomes.¹⁶ Clinical data are stored and retrieved by means of Oxford Medical Information Systems (OX-MIS) and Read codes for diseases or causes of morbidity and mortality that are cross-referenced to the International Classification of Diseases (ICD-9). Several independent validation studies have shown that the GPRD database has a high level of completeness and validity, including hip fractures.^{17,18}

The PHARMO RLS (www.pharmo.nl) includes the demographic details and complete medication history of 950,000 community-dwelling residents of more than 25 population-defined areas in the Netherlands from 1986 onwards. It is further linked to hospital admission records as well as several other health registries, including pathology, clinical laboratory findings and general practitioner data. Since the majority of all patients in the Netherlands are registered only with one community pharmacy, independently of prescriber, pharmacy records are virtually complete with regard to prescription drugs. For this study, drug dispensing and hospitalisation data were used. The computerised histories record information on the type of drug dispensed, dispensing date, prescriber, amount dispensed and prescribed dosage regimen. Hospital discharge records include detailed information on the primary and secondary discharge diagnoses, diagnostic, surgical and treatment procedures, type and frequency of consultations with medical specialists and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, 9th edition (ICD-9-CM).¹⁹

Definition of cases and controls

GPRD

A case-control study was conducted using GPRD data collected from January 1987 to July 1999. The details of this study have been described elsewhere.^{20,21} Briefly, cases were defined as patients aged 18 years and older with a first record of a hospital admission for a hip/femur fracture (ICD-9 codes 820-821) recorded in their medical records between the enrolment date of their practice in the GPRD and the end of data collection. The date of the occurrence of the hip/femur fracture was the index date. Each case was matched by year of birth, sex, medical practice and calendar time, to one control patient without a history of a fracture. If no eligible control was available, the age criterion was expanded consecutively at one-yearly intervals to a maximum of ten years. If no eligible

control patient could be found, then an age- and sex-matched control patient from another practice was selected.

PHARMO RLS

Cases were patients aged 18 years and older with a first admission for a hip/femur fracture between 1 January 1991 and 31 December 2002. The date of the hospital admission was the index date. Up to four control patients, who did not have a history of any type of fracture, were matched to each case by year of birth, gender, region, and calendar time.

Exposure assessment

For each patient, we identified all prescriptions (GPRD) and dispensings (PHARMO RLS) of beta-blockers prior to the index date. Current users were defined as patients who had a prescription/dispensing for beta-blockers within three months prior to the index date. Recent users received a last prescription/dispensing between three to six months before the index date, past users between six and 12 months before the index date, whereas distant past users had a last prescription more than 12 months before the index date. The last prescribed daily dose prior to the index date was obtained from the written dosage instructions. For each patient, cumulative exposure to beta-blockers ever before the index date was calculated. The effect of cumulative dose was assessed both regardless of the timing of use and stratified to current, recent, past and distant past use. Thus, current users could be classified to a low previous cumulative exposure (e.g. 1-2 30-day prescriptions), or a high previous cumulative exposure (e.g. 100 30-day prescriptions). The estimated daily dose for each class of beta-blocker was expressed as a fraction of the WHO defined daily dose (DDD). A DDD is defined the assumed average maintenance dose per day for a drug if used for its main indication in adults.²² DDD-equivalents can be used to compare drugs within a certain therapeutic group. In this study, we converted the DDD-equivalents to milligrams of metoprolol, similar to the approach used in previous studies.²¹ Furthermore, beta-blockers were categorised according to receptor selectivity and lipophilicity based on data in handbooks on clinical pharmacology and therapeutics.

Statistical analysis

The strength of the association between use of beta-blockers and risk of hip/femur fractures was estimated using conditional logistic regression analysis (SAS version 9.1.3, PHREG procedure) and expressed as odds ratios (OR) and 95% confidence intervals (CI). Fi-

nal regression models were determined by stepwise backward elimination using a significance level of 0.05. Smoothing spline regression plots were used to visualise the effect of cumulative beta-blocker dose on risk of hip/femur fractures.²³

In our analysis, we controlled for a wide range of clinical variables that have been associated with risk of falls or fractures. In the GPRD study, we included the following variables in the final model: history of diabetes mellitus, rheumatoid arthritis, hyperthyroidism, congestive heart failure, seizures, anemia, dementia, depression, psychotic disorder, cerebrovascular accident, chronic obstructive pulmonary disease, osteoporosis, and a record of back pain or falls in the year before the index date. Furthermore, prescriptions, in the six months prior to the index date, for anticonvulsants, nonsteroidal anti-inflammatory drugs (NSAIDs), methotrexate, hormone replacement therapy (HRT), other antihypertensive drugs (low-ceiling diuretics, Renin Angiotensin Aldosterone System (RAAS) inhibitors, calcium channel blockers), anxiolytics/hypnotics, antipsychotics, antidepressants, anti-Parkinson drugs, oral corticosteroids (OCs), inhaled corticosteroids (ICS), bronchodilators, and body mass index were retained in the model. In the PHARMO RLS study, variables included in the final model were a dispensing of benzodiazepines in the three months prior to the index date, or in six months prior to the index date, a dispensing of OCs, ICS, bronchodilators, statins, BMD modifying drugs, HRT, antipsychotics, antidepressants, opioids, antiepileptics, other antihypertensive drugs (low-ceiling diuretics, RAAS inhibitors, calcium channel blockers), antidiabetics, laxants, DMARDs, NSAIDs and metoclopramide. A history of hospital admission for cerebrovascular disease, cancer, endocrine disorders, inflammatory bowel disease (IBD), obstructive airway disease, musculoskeletal and connective tissue diseases, anaemia and skin diseases prior to the index date were also included in the final model.

Results

The study population in the GPRD comprised 22,247 cases and 22,247 controls, whereas in the PHARMO RLS 6,763 cases and 26,341 controls were identified. The characteristics of both populations are displayed in Table 2.2.1. The sex and age distributions of cases were similar in the two case-control sets, although more cases in the GPRD set were aged over 80 years.

Current use of beta-blockers was associated with a significantly decreased risk of hip/femur fracture in both databases, whereas recent and past use was not (Table 2.2.2).

Table 2.2.1 Baseline characteristics of the GPRD and PHARMO RLS.

Characteristic	GPRD		PHARMO RLS	
	Cases (n=22,247)	Controls (n=22,247)	Cases (n=6,763)	Controls (n=26,341)
Number of women	75.8%	75.8%	72.9%	72.7%
Age (years)				
< 65	13.9%	13.9%	15.8%	16.2%
65-79	30.8%	32.2%	36.6%	37.3%
≥ 80	55.2%	53.9%	47.6%	46.5%
Smoking status ^a	22.1%	20.6%	no data available	
BMI^b				
20-25	46.6%	42.4%	no data available	
<20	18.0%	9.7%		
>25	35.4%	47.9%		
Use of prescription drugs (in 6 months before index date)				
Antidepressants	13.0%	7.2%	9.5%	5.1%
OCs	7.2%	4.4%	5.4%	3.5%
Thiazide diuretics	11.9%	12.9%	12.1%	11.4%
Nitrates	6.9%	7.4%	9.4%	9.1%
HRT	0.6%	1.2%	1.1%	1.3%

a No data on smoking status for 45% of GPRD study population.

b No data on body mass index for 58.5% of GPRD study population.

BMI: body mass index; OC: oral corticosteroid; HRT: hormone replacement therapy.

Adjusted ORs for current beta-blockers users were 0.83 [95% CI: 0.75-0.92] in the GPRD and 0.87 [95% CI 0.80-0.95] in the PHARMO RLS. There was no strong effect of cumulative dose among current users of beta-blockers in either data set (Figure 2.2.1), while assessing the effect cumulative dose irrespective of timing of use yielded the similar results. The most frequently prescribed beta-blocker in the GPRD was atenolol (3.0% among cases vs. 4.0% among controls, adjusted OR 0.80 [95% CI 0.71-0.90]. Current use of other beta-blockers was infrequent (propranolol 0.4% vs. 0.5%, metoprolol 0.2% vs. 0.2%) and not associated with a decreased risk of hip/femur fracture: adjusted OR 0.90 [95% CI 0.76-1.06]. In the PHARMO RLS, the most frequently used beta-blockers at the index date was metoprolol (4.6% among cases vs. 5.6% among controls), atenolol (3.2% vs. 3.6%), sotalol (1.9% vs. 1.5%) and propranolol (0.9% vs. 0.9%). The adjusted ORs for current use of metoprolol and atenolol were 0.79 [95% CI 0.69-0.90] and 0.89 [95% CI 0.77-1.04]. Current use of propranolol (adjusted OR 0.98 [95% CI 0.74-1.21]) and sotalol (adjusted OR 1.15 [95% CI 0.93-1.42]) were not associated with a protective effect of hip/femur fracture. Categorizing beta-blockers according to their lipophilicity, receptor selectivity or last prescribed daily dose did not reveal major differences in effect (Table 2.2.2), nor did stratification according to age and gender (Table 2.2.3).

The protective effect of beta-blockers was only present among patients who had been treated with other antihypertensive agents (such as low-ceiling diuretics, calcium antagonists, RAAS-inhibitors), either concurrently or in the past (Table 2.2.3). This finding was consistent in both GPRD (adjusted OR 0.73 [95% CI 0.64-0.83] and the PHARMO RLS (adjusted OR 0.76 [95% CI 0.67-0.86].

Table 2.2.2 Use of beta-blockers and risk of hip/femur fracture in the GPRD and PHARMO RLS.

Exposure to beta-blockers	GPRD				PHARMO RLS			
	Cases (%)	Controls (%)	Crude OR (95% CI)	Adjusted OR (95% CI) ^a	Cases (%)	Controls (%)	Crude OR (95% CI)	Adjusted OR (95% CI) ^a
Current use	4.5%	5.9%	0.70 (0.64-0.77)	0.82 (0.74-0.91)	12.4%	13.7%	0.91 (0.83-0.98)	0.87 (0.80-0.95)
Recent use	0.6%	0.6%	0.89 (0.70-1.14)	0.88 (0.68-1.15)	1.7%	1.7%	1.01 (0.82-1.24)	0.93 (0.75-1.15)
Past use	0.7%	0.6%	1.10 (0.86-1.40)	0.99 (0.76-1.28)	1.4%	1.3%	1.11 (0.88-1.40)	0.99 (0.78-1.26)
Distant past use	3.7%	2.8%	1.10 (0.98-1.22)	1.06 (0.94-1.20)	6.8%	6.3%	1.07 (0.96-1.20)	0.97 (0.87-1.09)
Among current users of beta-blockers								
Selectivity^b								
Low	1.0%	1.2%	0.75 (0.63-0.90)	0.86 (0.71-1.05)	3.5%	3.1%	1.12 (0.97-1.30)	1.04 (0.89-1.21)
Medium	0.1%	0.2%	0.79 (0.48-1.32)	0.81 (0.47-1.41)	0.3%	0.5%	0.40 (0.20-0.84)	0.38 (0.18-0.79)
High	3.3%	4.4%	0.69 (0.62-0.76)	0.77 (0.69-0.87)	8.7%	10.1%	0.86 (0.79-0.95)	0.84 (0.76-0.93)
Lipophilicity^c								
Hydrophile	3.2%	4.2%	0.69 (0.62-0.77)	0.78 (0.70-0.88)	5.1%	5.2%	0.98 (0.86-1.11)	0.94 (0.83-1.06)
Intermediate	0.2%	0.2%	0.77 (0.50-1.20)	0.88 (0.56-1.39)	0.5%	0.4%	1.15 (0.77-1.73)	1.04 (0.69-1.58)
Lipophile	1.1%	1.4%	0.72 (0.60-0.85)	0.81 (0.68-0.98)	6.9%	8.0%	0.85 (0.77-0.95)	0.83 (0.74-0.92)
First prescription								
Yes	0.2%	0.2%	0.93 (0.58-1.48)	1.18 (0.69-1.99)	0.4%	0.6%	0.63 (0.42-0.95)	0.62 (0.41-0.94)
Last prescribed daily dose^d								
<0.67 DDD	0.9%	1.2%	0.72 (0.59-0.87)	0.81 (0.65-1.00)	8.7%	9.8%	0.89 (0.81-0.98)	0.87 (0.79-0.96)
0.67-1.33 DDD	2.0%	2.6%	0.73 (0.64-0.83)	0.85 (0.74-0.99)	3.2%	3.4%	0.95 (0.82-1.11)	0.90 (0.77-1.06)
> 1.33 DDD	1.4%	2.0%	0.64 (0.55-0.75)	0.81 (0.69-0.97)	0.4%	0.4%	0.95 (0.61-1.49)	0.85 (0.54-1.35)

a: Adjusted for use of other antihypertensive drugs and general risk factors for falls and fractures (see Methods section).

b/c: Selectivity and lipophilicity of the most recent prescription before index date were classified according to data from seminal pharmacology handbooks.

d: One DDD is equivalent to 150 mg metoprolol.

Table 2.2.3 Current use of beta-blockers and risk of hip/femur fractures in patient subgroups.

Current use of beta-blockers	GPRD				PHARMO RLS			
	Cases (%) ^a	Controls (%) ^a	Crude OR (95% CI)	Adjusted OR (95% CI) ^b	Cases (%) ^a	Controls (%) ^a	Crude OR (95% CI)	Adjusted OR (95% CI) ^b
Gender								
Men	3.4%	4.5%	0.68 (0.55-0.84)	0.77 (0.60-0.98)	10.1%	12.0%	0.83 (0.70-0.98)	0.77 (0.64-0.93)
Women	4.8%	6.3%	0.71 (0.64-0.78)	0.83 (0.74-0.93)	13.3%	14.4%	0.93 (0.95-1.02)	0.90 (0.82-1.00)
Age (years)								
<65	2.9%	3.1%	0.93 (0.68-1.26)	0.91 (0.62-0.91)	5.0%	7.2%	1.04 (0.80-1.35)	0.94 (0.70-1.27)
65-80	7.0%	9.1%	0.71 (0.62-0.80)	0.84 (0.73-0.98)	14.5%	16.8%	0.84 (0.58-1.12)	0.80 (0.70-0.91)
≥80	3.5%	4.6%	0.65 (0.57-0.75)	0.77 (0.66-0.91)	12.4%	13.5%	0.94 (0.84-1.06)	0.94 (0.83-1.07)
History of anti-hypertensive drug use								
No	2.2%	2.4%	0.89 (0.77-1.04)	0.97 (0.82-1.14)	8.3%	8.1%	1.02 (0.85-1.23)	1.01 (0.90-1.14)
Yes	9.7%	14.7%	0.60 (0.53-0.67)	0.73 (0.64-0.83)	20.9%	26.9%	0.73 (0.65-0.83)	0.76 (0.67-0.86)

a: Percentages represent the proportion of current beta-blocker within each subcategory (e.g. male gender).

b: Adjusted for use of other antihypertensive drugs and general risk factors for falls and fractures (see Methods section).

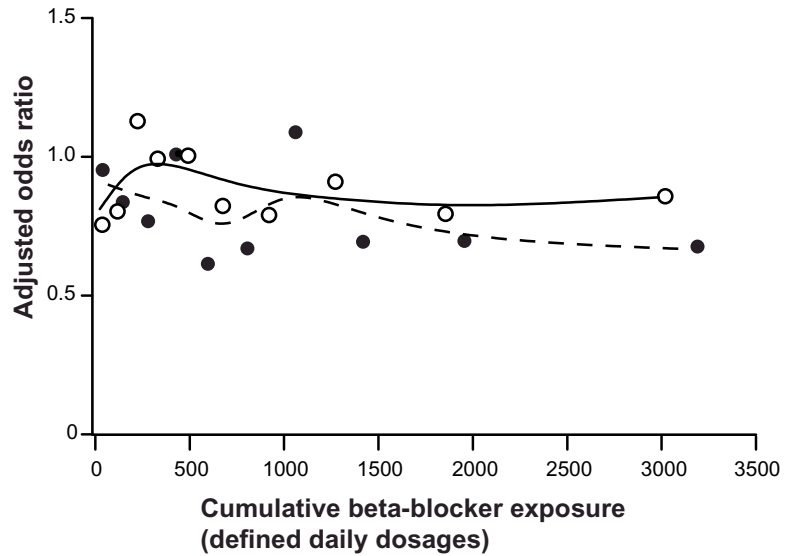


Figure 2.2.1 Spline visualisation of cumulative dose among current beta-blocker users and risk of hip/femur fractures (GPRD - dashed line, solid circles; PHARMO RLS - solid line, open circles). Cumulative dose is expressed in DDDs, 1000 DDDs are equivalent to 150 grams of metoprolol). Odds ratios were adjusted for the same confounders as in Table 2.2.2, except for the use of antihypertensive drugs.

Among patients using only beta-blockers, the adjusted ORs were close to unity. In both datasets, the interaction term between current use of beta-blockers and use of other antihypertensive drugs was statistically significant ($p < 0.05$). Furthermore, no effect of cumulative dose was found in either current users of beta-blocker only or in current beta-blocker users with a history of using other antihypertensive drugs (Figure 2.2.2). Further stratification according to high or low average daily dose during the study period indicated no effect of the intensity of beta-blocker use on the risk estimates.

Discussion

In both GPRD and PHARMO RLS data sets, current use of beta-blockers was associated with a decreased risk of hip/femur fractures. However, there was no reduced risk of hip/femur fractures among patients who did not have a history of using other antihypertensive drugs: a protective effect of beta-blockers was only observed for patients with current or prior use of other

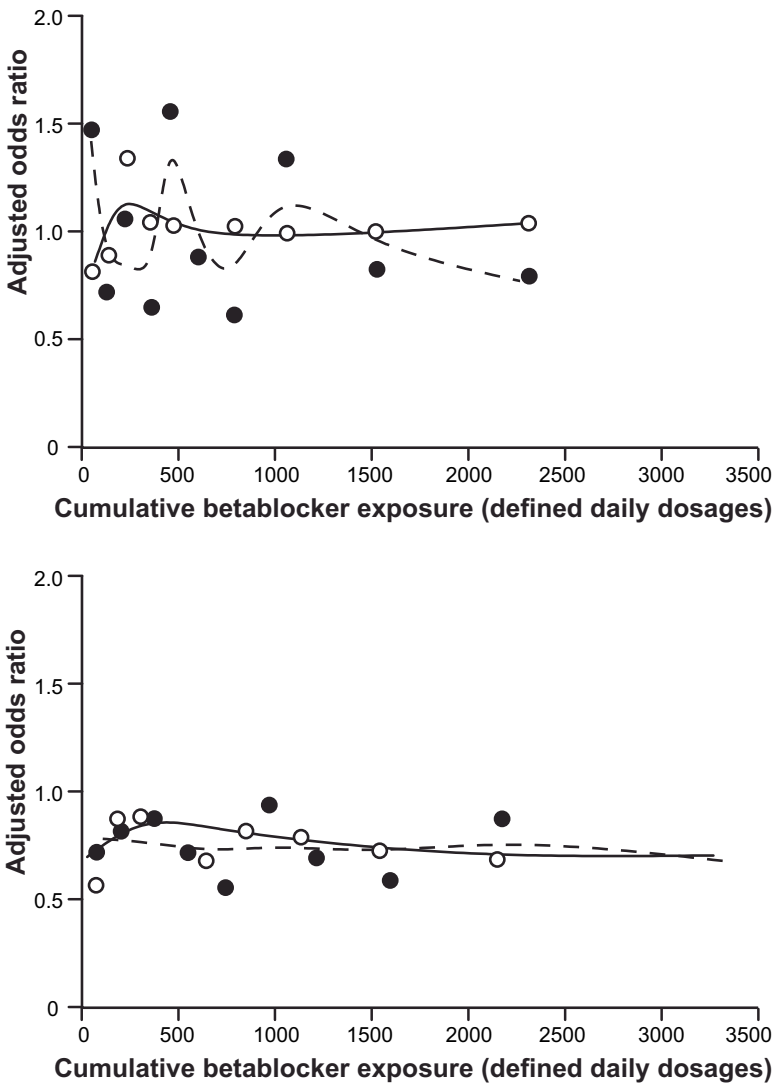


Figure 2.2.2 Spline visualisation of cumulative dose among current beta-blocker users, stratified according to patients not having (top) or having a history of other AHT (bottom) (GPRD: dashed line, solid circles; PHARMO RLS: solid line, open circles). Cumulative dose is expressed in DDDs, 1000 DDDs are equivalent to 150 grams of metoprolol). Odds ratios were adjusted for the same confounders as in Table 2.2.2, except for the use of antihypertensive drugs.

antihypertensive agents. Even within this group of patients, no dose-response relationship with beta-blocker use was found.

The effect was constant with cumulative dose and the OR was below 1.0 even among patients who just started treatment with beta-blockers. As the mechanism by which beta-blockers could influence BMD is likely to need some time to exert a clinically relevant effect, this finding suggests that the association between beta-blockers and fracture risk is not causal.

Based on in-vivo and in-vitro studies and the discovery that the central nervous system is involved in the regulation of bone, beta-blockers have been implicated in a preventive role in patients with osteoporosis. Central effects of leptin have been found to be mediated by the sympathetic nervous system, acting via beta-2 receptors on osteoblasts.³ Beta-2 agonists stimulate bone-resorption activity in osteoclasts.²⁴ Data from mice studies showed that systemic application of beta-2 agonists had a negative effect on bone mass,²⁵ whereas non-selective beta-blockers stimulated bone formation in rats.⁶

Several epidemiological studies have reported discrepant results on the association between use of beta-blockers and risk of fracture,⁷⁻¹² including a study that also used data from the GPRD.⁸ The reason for the discrepancy is unclear. Emerging data from randomised controlled trials also support a lack of effect of beta-blockers on the risk of fracture. Recently, a clinical trial among 41 normal postmenopausal women found no evidence that propranolol stimulates bone formation, as measured by bone turnover markers.²⁶ Furthermore, pooled data from nine clinical trials investigating the non-selective beta-blocker carvedilol in the management of congestive heart failure did not provide evidence in support of an effect of beta-blockers on fracture risk reduction.¹⁰ The data from this meta-analysis is consistent to the results of our study, as no effect on fracture was observed in patients treated with beta-blockers without history of other antihypertensive drug use.

Therapeutic uses of beta-blockers include the treatment of hypertension, as well as heart failure, secondary prevention post-MI, cardiac dysrhythmias, and angina pectoris. Cardiovascular disease, heart failure and hypertension have all been associated with low BMD.²⁷⁻³⁰ Because thiazide diuretics, calcium channel blockers and inhibitors of the renin-angiotensin system have also been associated with beneficial effects on bone³¹, we have chosen to stratify in our study on history of use of other antihypertensive drugs to separate the effect of current use of beta-blockers from that of other antihypertensive agents. This method of stratification was not

applied in earlier epidemiological studies on beta-blockers and fractures.

The strength of our study is that it was population-based. Furthermore, we found the same results in both the UK and the Dutch data sets. The prevalence of beta-blocker use was nearly three times as high in the PHARMO RLS compared to the GPRD. In 2002, 5.1 million prescriptions for beta-blockers were issued in the Netherlands (population 16 million),³² compared to 22.4 million prescriptions in the UK in the same year (population 59 million).³³ Taking into account that prescriptions in the UK are usually for 30 days and in the Netherlands for 90 days, we can conclude that the observed difference in exposure prevalence is in line with prescribing data volumes in both countries.

Observational studies like ours have potential for bias and confounding and can fuel debates on study interpretation and credibility.³⁴⁻³⁶ Various drugs with effects on the central nervous system are known to increase the risk of falls and thereby fracture risk. Also, there are likely to be complex interactions between vascular disease and fracture risk, operating through falls risk, BMD, or common genetic or lifestyle factors. In this study we had no information on BMD and we cannot exclude the possibility that cases and controls were different with respect to BMD. However, given that start of antihypertensive treatment in daily clinical practice will usually be independent of patient BMD, major confounding seems unlikely. Although variables included in the final regression models were slightly different between both datasets, due to the nature of the data collections, multivariate adjustment had only modest effects on the OR of the exposure of interest. Information on smoking and BMI was not available in the PHARMO RLS database, but adjustment for these factors in the GPRD had no influence on risk estimates (smoking was not retained in the model). Data on BMI was missing for 58% of the GPRD study population, so we cannot exclude the concern that adjustment was suboptimal. We had no data on physical activity, diet or socio-economic status, as such information is not available in both databases used in our studies.³⁷ Furthermore, we cannot exclude the possibility that residual confounding can explain part of our results.

An alternative explanation for our findings could be that the protective effect of beta-blockers on fractures is an artifact caused by selective under-use in patients with an unmeasured comorbidity, a problem that has been described by Glynn et al in a study on cardiovascular drug use and mortality.³⁸ In their study among elderly subject in the US, they found that users of drugs from seven commonly prescribed therapeutic classes, including

beta-blockers, thiazide diuretics and ACE inhibitors, had reduced rates of death compared to non-users, which was more likely to be explained by selective prescribing and non-adherence. A potential limitation of our study is that we confined our study to hip/femur fractures and did not evaluate other type of fractures. It is possible that potential beneficial effects of beta-blockers are present only at sites other than the hip/femur, but there is no evidence to support this.

In conclusion, the reduction in hip/femur fracture risk was not related to cumulative dose of beta-blockers and is only present in patients using beta-blockers with a history of using other anti-hypertensive drugs as well. This suggests that the effect of beta-blockers on hip/femur fracture is not causal.

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Chapter 3.1

Fracture Risk with Intermittent High-Dose Oral Corticosteroid Therapy

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Summary

Objective. To evaluate the risk of fracture in patients receiving intermittent therapy with high-dose oral corticosteroids (OCs).

Methods. The study group comprised 191,752 patients from the UK General Practice Database who were 40 years of age and older and received therapy with OCs. The follow-up time period was divided into the categories of “current” and “no exposure.” The daily dose and cumulative dose for each time period were determined. Relative risks were estimated using Cox proportional hazards models, adjusted for age, sex, body mass index, smoking, disease history, and drug history. Fractures of the radius/ulna, humerus, rib, femur/hip, pelvis, or vertebrae were included in the evaluation.

Results. Patients who intermittently received high-dose OCs (daily dose ≥ 15 mg) and had no or little previous exposure to OCs (cumulative exposure ≤ 1 g) had a small increased risk of osteoporotic (but not hip/femur) fracture; this risk increased substantially with increasing cumulative exposure. Among patients who received a daily dose ≥ 30 mg and whose cumulative exposure was >5 g, the relative risk (RR) of osteoporotic fracture was 3.63 (95% confidence interval [95% CI 2.54-5.20]), the RR of fracture of the hip/femur was 3.13 [95% CI 1.49-6.59], and the RR of vertebral fracture was 14.42 [95% CI 8.29-25.08].

Conclusion. Intermittent use of high-dose OCs (daily dose ≥ 15 mg and cumulative exposure ≤ 1 g) may result in a small increased risk of osteoporotic fracture. Conversely, patients who receive several courses of high-dose OCs (daily dose ≥ 15 mg and cumulative exposure >1 g) have a substantially increased risk of fracture.

Introduction

Oral corticosteroids (OCs) are frequently prescribed to patients with inflammatory disorders, such as obstructive airway disease, rheumatoid arthritis (RA), and inflammatory bowel disease (IBD). Treatment with OCs has been associated with increases in the risk of fractures, particularly fractures of the hip and vertebrae.¹⁻³ This effect is dose dependent and occurs rapidly after the start of treatment.²⁻⁴ However, previous studies have not distinguished between the effect on fractures of intermittent therapy and long-term therapy with OCs. Several studies have evaluated the association between intermittent use of high-dose OCs and bone mineral density (BMD). A study in patients with Crohn's disease demonstrated a rapid loss of BMD following short-term treatment with OCs, but this effect was not observed in 3 other studies.⁵⁻⁸ Those studies included only a small number of patients and differed in terms of the extent of OC exposure. Importantly, fracture is the clinically more important endpoint, and it has been reported that the risk of fracture in patients receiving OCs may be partially independent of BMD.¹ The objective of the current study was to evaluate the risk of fracture in patients receiving intermittent treatment with high-dose OCs.

Methods

We conducted a retrospective cohort study among patients from the UK General Practice Research Database (GPRD). The GPRD contains computerised medical records, prescription data, specialist referrals, and hospital discharge summaries of patients enrolled in 683 general practices in England and Wales.⁹ A cohort of patients aged 40 years and older, all of whom received OCs between January 1987 and December 1997, was created. This cohort was previously analysed,¹⁰ but that analysis focused on the effects of continuous use of OCs on the risk of fractures, with the daily dose of OCs averaged over the total treatment period.

Because patients may change their daily dose of OCs over time, and because high doses of OCs are used for only short periods of time, the current analysis evaluated the association between the daily dose of OCs and fracture risk, using time-dependent analyses and correlating the daily dose for each OC treatment episode to the risk of fracture. In addition, the current study compared patients currently receiving OCs with patients who had received OCs in the past, while our previous study compared patients receiv-

ing OCs with controls. This approach was used in order to minimise confounding by indication.

Assessment of exposure and outcome

In this study, the daily dose of OCs was estimated separately for each OC prescription. The total period of follow-up for each patient was taken as the time period from the first OC prescription until the end of data collection for the GPRD. This total period of time was then divided into periods of current exposure and past exposure, with patients moving between current and past exposure. Each period of current exposure started with an OC prescription and ended three months after the expected duration of OC therapy. The expected duration of OC therapy was based on how the drug was supplied and the prescribed daily dose (as determined by instructions from the patient's general practitioner). In cases in which patients received a repeat prescription within a current exposure period, this period was then extended using the expected duration of the repeat prescription. In the event of overlap between two prescriptions (i.e. a repeat prescription given within the duration of use for a previous prescription), the "overlap" days were added to the duration of the repeat prescription. When data on the total drug supply or daily dose were missing, the median expected duration of treatment (based on data for patients of similar age and sex) was used.

At the time that each course of OCs was prescribed, the prior cumulative OC exposure within the current exposure period was calculated. We assumed that a period of intermittent use was characterised by high daily doses and low cumulative exposure. Each patient was followed up until he or she sustained a clinical osteoporotic fracture (i.e. a fracture of the radius/ulna, femur/hip, vertebra, humerus, or pelvis) following the first OC prescription, or until the patient's change of practice, death, or the end of the study (whichever came first).

Assessment of covariates

The following risk factors were considered as potential confounders: prior prescriptions for anticonvulsants, antiarrhythmics, hypnotics/anxiolytics, antidepressants, antiparkinson drugs, or non-steroidal anti-inflammatory drugs (NSAIDs), and the occurrence of falls six months prior to the OC prescription. In addition, a history of cerebrovascular disease, dementia, fractures, or anemia prior to the OC prescription was evaluated as a potential confounder. Smoking status and body mass index were also determined.

Statistical analysis

Cox proportional hazards models were used to estimate the relative risk (RR) of fracture. The past exposure periods were considered the reference category, in order to minimise confounding by indication. Spline regression analyses were used to summarise the association between time between repeat OC prescriptions and the risk of fractures. This method has been advocated as an alternative to categorical analysis.¹¹ All analyses were performed using SAS version 9.1.3 software (SAS Institute, Cary, NC).

Results

Baseline characteristics of the study subjects are shown in Table 3.1.1. The cohort included 191,752 patients who received OCs, of whom 111,349 (58.1%) were women. During and after therapy, patients who received OCs sustained a total of 7,412 osteoporotic fractures, of which 2,144 were hip/femur fractures and 1,269 were vertebral fractures. A total of 114,125 patients had received at least one prescription for a daily dose of ≥ 15 mg. The mean age of patients who received high-dose OCs was 64 years, and the most frequent indication for OC treatment was obstructive airway disease.

As shown in Table 3.1.2, patients receiving OCs at a dosage of <7.5 mg/day had a 60% increased risk of osteoporotic fracture. With a daily dose of 7.5–15 mg, this risk was increased by 115%, when compared to past use. Further increases in the daily dose were not associated overall with larger increases in risk (the

Table 3.1.1 Baseline characteristics of 191,752 oral corticosteroid (OC) users.

Characteristic	At least 1 prescription for <15 mg OCs (n=131,259)		At least 1 prescription for ≥ 15 mg OCs (n=114,125)	
Female gender	77,027	58.7%	65,245	57.2%
Age at baseline, years				
40–59	42,032	32.0%	40,116	35.2%
60–79	65,309	49.8%	56,473	49.5%
≥ 80	23,918	18.2%	17,536	15.4%
Diseases requiring oral corticosteroids				
Obstructive airway disease	64,312	49.0%	61,663	54.0%
Polymyalgia rheumatica	11,822	9.0%	7,332	6.4%
Inflammatory Bowel Disease	7,006	5.3%	4,902	4.3%
Rheumatoid Arthritis	6,859	5.2%	2,525	2.2%
Drug use 6 months before the first oral corticosteroid prescription				
Bronchodilators	54,701	41.7%	50,291	44.0%
NSAIDs	25,177	19.2%	19,731	17.3%
Hypnotics/anxiolytics	22,624	17.2%	18,495	16.2%
Rectal corticosteroids	2,390	1.8%	1,776	1.6%

risk of osteoporotic fractures was increased by 62% overall in patients receiving a daily dose ≥ 15 mg). In patients who received high-dose OCs (≥ 15 mg/day), a strong association with cumulative OC exposure was observed. Patients who intermittently received high-dose OCs but who previously had no or low cumulative exposure to OCs (daily dose ≥ 15 mg and cumulative exposure ≤ 1 g) had a small increased risk of osteoporotic and vertebral fracture (but not hip/femur fracture), while the risk increased substantially in patients with high cumulative exposure (Figure 3.1.1). Among patients who were receiving a daily dose ≥ 30 mg and whose cumulative exposure was >5 g, the RR was 3.63 [95% confidence interval (95% CI) 2.54-5.20] for osteoporotic fracture, 3.13 [95% CI 1.49-6.59] for hip/femur fracture, and 14.42 [95% CI 8.29-25.08] for vertebral fractures.

New users of high-dose OCs did not have a significantly increased risk of osteoporotic fracture (RR 0.97 [95% CI 0.81-1.16]). This risk was still not significantly increased among patients who received 1-4 prescriptions for OCs (RR 1.21 [95% CI 0.92-1.59] before the start of a new treatment episode, whereas patients who received more than four previous OC prescriptions had a significantly increased risk of osteoporotic fracture (RR 1.51 [95% CI 1.19-1.92]).

An analysis of the time since discontinuation of OC therapy showed that the RR of fracture was not increased in patients who had stopped receiving high dose OCs more than 12 months previously. Moreover, we observed a rapid decrease in the fracture risk beginning three months after discontinuation of treatment (Figure 3.1.2). Among patients who received low-dose OCs (<15 mg/day), the risk of fracture was no longer increased in those who had received their most recent prescription for OCs at least nine months previously (RR 1.23 [95% CI 0.90-1.70]). Figure 3.1.3 shows the risk of osteoporotic fracture among users of high-dose OCs who had high cumulative exposure or low cumulative exposure. The risk of fracture returned to baseline levels after six months in patients who were exposed to ≤ 1 g of prednisolone equivalent. In contrast, patients who received high-dose OCs and were exposed to >1 g of prednisolone equivalent were not at increased risk of fracture if they had received their last prescription at least 15 months before the index date.

Table 3.1.3 shows the RR of fracture, stratified according to the indication for OC therapy. No substantial differences were observed between the indications for OCs in terms of the risk of fracture. Patients who received a daily dose ≥ 15 mg and whose

cumulative exposure was >5 g had a three-fold increased risk of osteoporotic fractures, regardless of the underlying disease.

Discussion

In this study, we observed that intermittent use of high doses of OCs was associated with only a small increase in the risk of osteoporotic fracture. Nevertheless, continued use of high-dose OCs (cumulative exposure >1 g of prednisone equivalent) was associated with substantially higher risks of fracture. We did not observe major increases in the risk of fracture when short-term OC treatment was given at least one year after previous treatment. There were also no substantial differences in the relative increases in fracture risk between patients with obstructive airway disease, those with arthropathies, and patients with IBD.

Table 3.1.2 Adjusted risk of fracture, according to daily dose of oral corticosteroids.^a

Oral corticosteroid exposure	Osteoporotic fracture		Hip/femur fracture		Vertebral fracture	
	Adjusted for age and sex only	Adjusted for age, sex and other factors ^b	Adjusted for age and sex only	Adjusted for age, sex and other factors ^b	Adjusted for age and sex only	Adjusted for age, sex and other factors ^b
Past use	1.00	1.00	1.00	1.00	1.00	1.00
Current use						
<7.5 mg/day	1.68 (1.60-1.76)	1.60 (1.52-1.68)	1.60 (1.46-1.76)	1.49 (1.36-1.63)	3.51 (3.08-3.99)	3.21 (2.81-3.65)
7.5-15 mg/day	1.60 (1.50-1.71)	1.53 (1.43-1.63)	1.51 (1.34-1.69)	1.40 (1.24-1.57)	3.16 (2.70-3.69)	2.89 (2.47-3.39)
≥15 mg/day	2.15 (1.97-2.34)	1.99 (1.82-2.16)	2.44 (2.11-2.82)	2.17 (1.87-2.51)	4.59 (3.79-5.57)	4.00 (3.29-4.86)
	1.62 (1.61-1.78)	1.55 (1.53-1.69)	1.49 (1.47-1.78)	1.42 (1.36-1.65)	3.61 (3.06-3.98)	3.32 (2.79-3.64)

a: Values are the relative risk (95% confidence intervals)

b: Vertebral fracture risk was adjusted for age, sex, body mass index, smoking status, a history of falls, fractures, anemia, cerebrovascular disease, hospitalisations for obstructive airway disease, rheumatoid arthritis, and irritable bowel disease, and treatment with nonsteroidal anti-inflammatory drugs, hypnotics/anxiolytics, or antidepressants six months before the OC prescription. The risk of hip/femur fracture was adjusted for all of the aforementioned confounders as well as a history of dementia and exposure to antiepileptics and antiparkinson medication six months previously. The risk of osteoporotic fracture was adjusted for all of the aforementioned confounders as well as use of antiarrhythmic agents six months previously.

Table 3.1.3 Adjusted risk of fracture according to fracture type, disease at baseline and oral corticosteroid exposure.^a

Current oral corticosteroid exposure					
Fracture type/disease at baseline	Past exposure	Daily dose	Daily dose ≥ 15 mg, by cumulative dose		
		<15 mg	1 g	1-5 g	>5 g
Osteoporotic					
Obstructive airway disease	1.00	1.69 (1.58-1.82)	1.32 (1.10-1.58)	1.85 (1.45-2.37)	3.00 (2.30-3.91)
Arthropathy		1.49 (1.36-1.63)	1.21 (0.90-1.63)	1.92 (1.46-2.53)	2.69 (2.01-3.59)
Inflammatory Bowel Disease		1.56 (1.27-1.91)	1.34 (0.75-2.40)	1.57 (0.86-2.85)	3.20 (1.93-5.30)
Hip/femur					
Obstructive airway disease	1.00	1.37 (1.18-1.58)	0.90 (0.58-1.39)	1.37 (0.78-2.38)	1.94 (1.03-3.65)
Arthropathy		1.41 (1.20-1.66)	0.79 (0.40-1.55)	1.64 (0.96-2.78)	2.44 (1.42-4.19)
Inflammatory Bowel Disease		0.95 (0.66-1.38)	0.99 (0.35-2.84)	0.35 (0.04-2.62)	1.77 (0.63-4.91)
Vertebral					
Obstructive airway disease	1.00	3.67 (3.08-4.36)	1.71 (1.08-2.73)	5.65 (3.74-8.53)	10.61 (6.98-16.12)
Arthropathy		3.24 (3.08-4.36)	1.38 (0.59-3.22)	8.12 (5.19-12.74)	10.13 (6.06-17.08)
Inflammatory Bowel Disease		2.89 (1.74-4.80)	1.45 (0.33-6.33)	6.06 (2.51-14.55)	11.58 (5.08-26.41)

a: Values are the relative risk (95% confidence intervals). Adjusted for the same confounders as in Table 3.1.2, footnote b.

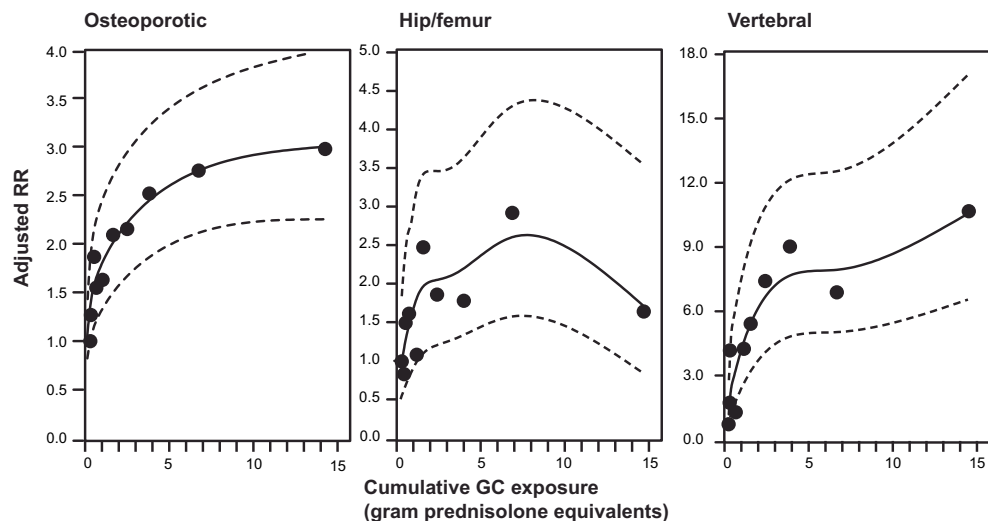


Figure 3.1.1 Relative risk (RR) of fracture in patients receiving high-dose (≥ 15 mg/day) oral corticosteroids (OCs) according to cumulative exposure, adjusted for age, sex, body mass index, smoking status, a history of falls, fractures, anemia, cerebrovascular disease, hospitalisations for obstructive airway disease, rheumatoid arthritis, and inflammatory bowel disease, and the use of nonsteroidal anti-inflammatory drugs, hypnotics/anxiolytics, or antidepressants six months before receiving a prescription for OCs. The risk of hip/femur and osteoporotic fracture was also adjusted for a history of dementia and exposure to antiepileptic or antiparkinson drugs six months previously. The risk of osteoporotic fracture was also adjusted for use of antiarrhythmic drugs six months previously. Solid lines represent the RR; dashed lines represent the 95% confidence intervals.

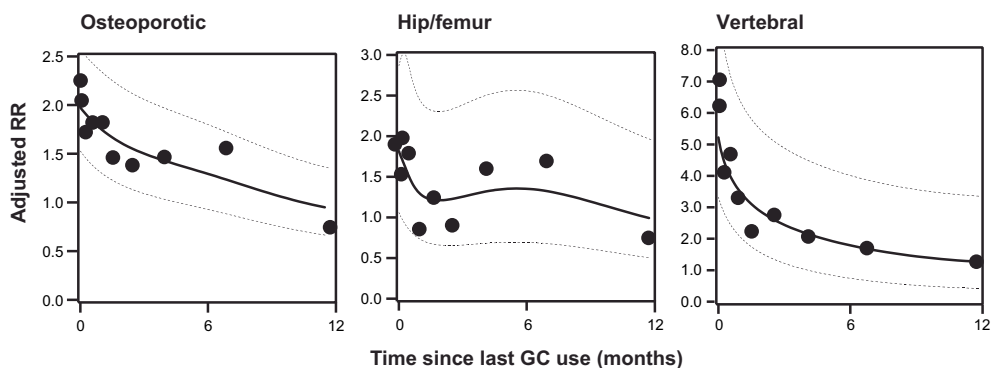


Figure 3.1.2 Relative risk (RR) of fracture in patients receiving high-dose (≥ 15 mg/day) oral corticosteroids (OCs), according to time since discontinuation of therapy. Solid lines represent the RR; dashed lines represent the 95% confidence intervals. See Figure 3.1.1 for a description of the adjustments made for the risk of vertebral, hip/femur, and osteoporotic fracture.

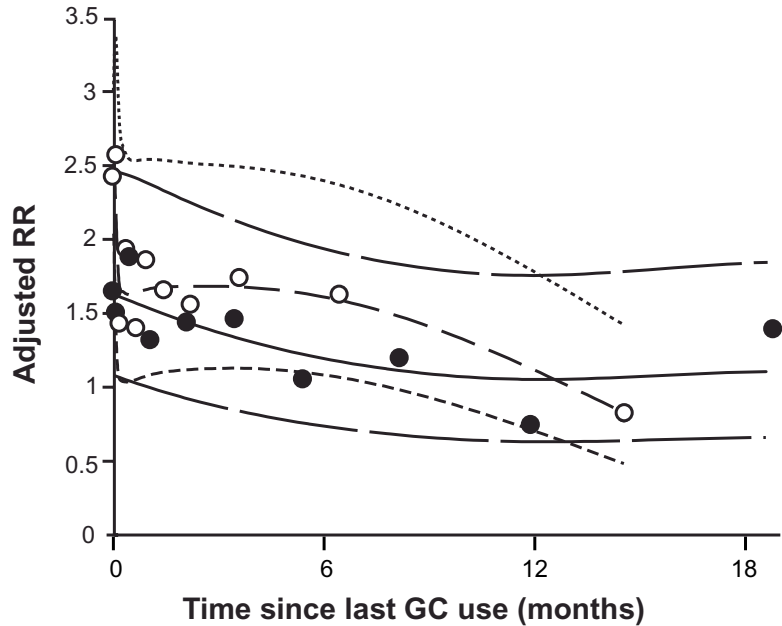


Figure 3.1.3 Relative risk (RR) of osteoporotic fracture in patients receiving high-dose (≥ 15 mg/day) corticosteroids (OCs) according to time since discontinuation of therapy, adjusted for age, sex, body mass index, smoking status, a history of falls, fractures, anemia, cerebrovascular disease, hospitalisations for obstructive airway disease, rheumatoid arthritis, and inflammatory bowel disease, and the use of nonsteroidal anti-inflammatory drugs, hypnotics/anxiolytics, antidepressants, or antiarrhythmic drugs six months before receiving a prescription for oral OCs. The solid line (—) and solid circles represent the RR in patients with low cumulative exposure (≤ 1 g prednisolone equivalent); broken lines (— — —) represent the 95% confidence interval. The dashed line (- - -) and open circles represent the RR in patients with high cumulative exposure (> 1 g prednisolone equivalent); dotted lines (- - - -) represent the 95% confidence interval.

The findings from this study extend previous results for the same study population.^{2,3} In earlier studies with our study population, daily doses of OCs were averaged over the total treatment period. The current study focused on the time of use of high-dose OCs. Consistent with our earlier investigations that focused on the effects of continuous treatment with OCs,³ in the current study we observed a strong association between daily dose of OCs and risk of fracture in patients who continuously received OCs. However, we also observed that this strong dose response did not apply to patients who received high doses of OCs for short periods of time or intermittently. We observed a small increased risk of osteo-

porotic or vertebral fracture among patients who received high-dose OCs and whose cumulative intake was 1 g of prednisone or less (intermittent users). The risk of hip/femur fracture was not increased.

To our knowledge, this is the first study to demonstrate that intermittent treatment with high-dose OCs may result in only a small increased risk of fractures. The current findings extend results from studies that evaluated the association between short-term, intermittent use of high-dose OCs and BMD.^{6-8,12} Reduced BMD is an independent risk factor for fracture.¹³ Intermittent use of high-dose OCs (daily dose ≥ 10 mg and cumulative exposure ≤ 1 g) did not change BMD in men with chronic obstructive pulmonary disease. In addition, significantly decreased femoral neck and lumbar spine BMD was observed after cumulative exposure >1 g of prednisone.⁵ Conversely, longer duration of OC treatment (1,260 mg, with tapering over 2 months) resulted in decreased femoral neck BMD in patients with Crohn's disease.⁸

The OC regimen corresponded with a daily dose of 22.5 mg, and these results are consistent with our observation of an increased risk of hip fracture with cumulative exposure >1 g among patients who received high-dose OCs. Although we already observed an increased risk of vertebral fracture among patients with obstructive airway disease who had received a cumulative dose of ≤ 1 g, our cumulative dose-response trend was similar to the cumulative exposure threshold of 1 g of prednisone with regard to the risk of hip fracture.

Several pathways have been suggested for accelerated bone loss and decreased bone formation rates leading to an increased risk of fracture in patients using OCs. Bone resorption may be facilitated by decreased absorption of calcium and phosphate in the gut and renal tubules, increased parathyroid hormone secretion, and increased osteoclastic activity. Decreased bone formation can be the result of decreased osteoblast and preosteoblast proliferation, sex steroid deficiency, and increased apoptosis of osteoblasts and osteocytes.^{14,15} However, the risk of fracture in patients receiving OCs is partially independent of a decreased bone mass¹, and the increased fracture risk associated with OCs may occur three months after treatment is initiated.² Increased apoptosis of osteoblasts and osteocytes and decreased osteocyte viability may lead to bone microdamage and, ultimately, bone fragility.¹⁶⁻¹⁹ Damage to the microarchitecture of trabecular bone has been shown to be a risk factor for vertebral deformities.²⁰ In addition, it has been suggested that the degree of disruption of the trabecular network of bone correlates with cumulative exposure to OCs.²¹ OC-induced disruption

is probably reversible, which is consistent with our observation of a rapid decrease in fracture risk 3-12 months after cessation of OCs.

Our study has several limitations. First, data regarding treatment with OCs during hospitalisation and treatment prior to the start of data collection for the GPRD were not recorded, which may have resulted in an underestimate of the effects of OCs. Second, information on smoking and body mass index was available for only part of the study population. Information on potential confounders such as diet and exercise was not available. Last, the comparison group in this study consisted of past users of OCs. This approach was used to reduce confounding by indication. Previously, it was demonstrated that fracture risk decreased rapidly toward baseline levels after discontinuation of OC therapy.³ A sensitivity analysis with stratification for past use according to “recent past” and “distant past” showed no substantial effect on the results. Thus, it is unlikely that any residual effects of OCs would have resulted in a substantive underestimate of the effects of OCs.

In conclusion, intermittent use of high-dose OCs (daily dose ≥ 15 mg and cumulative exposure ≤ 1 g) may result in a small increased risk of osteoporotic fracture. Conversely, patients who receive several courses of high-dose OCs (daily dose ≥ 15 mg and cumulative exposure > 1 g) are at substantially increased risk of fracture. Further investigations and preventative treatment might be conveniently targeted to these patients.

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Chapter 3.2

Severity of Obstructive Airway Disease and Risk of Osteoporotic Fracture

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Summary

Background. The use of inhaled corticosteroids has been associated with a dose-related increased risk of fracture. This may be related to systemic absorption. However, several studies have found that patients with more severe reductions in pulmonary function had reduced bone mineral density, independent of inhaled corticosteroids. The objective of this study was to evaluate the relationship between disease severity and fracture risk.

Methods. A large case-control study (108,754 cases) was conducted using data from the UK General Practice Research Database.

Results. It was found that higher doses of inhaled corticosteroids were associated with greater risks of fracture. The crude odds ratio of fracture among patients exposed to $>1,600$ μg beclomethasone equivalents per day was 1.95 [95% confidence interval (CI) 1.68-2.27]. When adjustments were made for disease severity and use of bronchodilators, the initial dose-response relationship between inhaled corticosteroids and fracture risk disappeared (adjusted OR of 1.19 [95% CI 1.01-1.41]).

Conclusion. Patients with severe obstructive airway disease are at risk of fracture. Adequate adjustment for disease severity is essential when the association between the use of inhaled corticosteroids and risk of osteoporotic fracture is studied in observational research.

Introduction

Inhaled corticosteroids (ICS) are frequently prescribed to patients with obstructive airway disease (OAD).¹ Although administered locally, ICS undergo systemic absorption and may induce a suppression of plasma cortisol, especially at higher doses.² Patients using oral corticosteroids have an increased risk of osteoporosis and fractures.² For users of ICS, an association between daily dose and increased risk of fractures has been reported.⁴⁻⁷ However, adjustment for underlying disease severity was limited in these studies. In the largest case-control study, adjustment for underlying disease severity was restricted to prior use of oral corticosteroids.⁵ The importance of controlling for severity of underlying disease in this type of research has recently been emphasised.^{8,9} Also, it has been reported that there was no increased risk of fracture in patients using ICS after adjustment for the presence of OAD or use of bronchodilators.^{10,11} Patients with OAD have been found to have a reduced bone mineral density (BMD), independent of the use of respiratory medication.¹²⁻¹⁴ Therefore, the objective of this study was to evaluate the relationship between disease severity of OAD and the risk of fracture.

Methods

Study population

A case-control study was conducted using data obtained from the General Practice Research Database (GPRD).¹⁵ This database comprises the entire computerised medical records of a sample of general practitioners in the UK. Several independent validation studies have confirmed a high level of completeness and validity of the GPRD with regard to the recording of fractures.^{16,17} In this study, cases were patients aged ≥ 18 years with a first record during GPRD follow-up (January 1987 to July 1999) of an osteoporotic fracture (defined as a fracture of the radius/ulna, femur/hip, ribs, humerus, vertebrae or clavicle).¹⁸ The date of the first fracture was defined as the index date. One control patient without a history of a fracture was matched to each case by age, gender, medical practice and calendar time. A history of OAD before the index date was examined in both cases and controls. The definitions for asthma and chronic obstructive pulmonary disease (COPD) were the same as those used in a previous GPRD validation study.¹⁹

Exposure

Use of medication for the treatment of OAD was examined, including bronchodilators (British National Formulary [BNF] Chapter 3.1 or 3.3) and ICS (BNF Chapter 3.2.)²⁰ Current users were patients who had received at least one prescription in the six months before the index date. Past users had received their last prescription more than six months prior to the index date. For each current user, the average daily dose of bronchodilators or ICS was estimated by dividing the total amount of respiratory medication by the treatment time (the time between the first and last prescription of respiratory medication). Dose equivalences were expressed as beclomethasone dipropionate equivalents (ICS) or salbutamol equivalents (bronchodilators, [salbutamol is a synonym of albuterol]). Equivalents of different compounds were calculated with defined daily doses.²¹

Indicators of more severe OAD included records of OAD exacerbations and oxygen use in the 12 months before the index date, respiratory problems (bacterial respiratory tract infections, coughing, presence of sputum, haemoptysis, dyspnoea, tachypnoea, shortness of breath, acute bronchitis or wheezing), use of oral corticosteroids in the six months before the index date and a body mass index (BMI) <20.

Next, the current authors controlled for various general risk factors of fracture, including history of diabetes mellitus, rheumatoid arthritis, hyperthyroidism, congestive heart failure, seizures, anaemia, dementia, depression, psychotic disorder and cerebrovascular accident. Moreover, prescriptions in the six months before the index date for anticonvulsants, nonsteroidal anti-inflammatory drugs (NSAIDs), methotrexate, hormone-replacement therapy, thiazide diuretics, anxiolytics/hypnotics, antipsychotics, antidepressants and anti-Parkinson's drugs were also considered as potential confounding variables. BMI and smoking status (current or ex-smoker, non-smoker or unknown) were included if entered in the database.

Statistical analysis

Odds ratios (ORs) of fracture were estimated using conditional logistic regression. Final regression models were determined by backward elimination using a significance level of 0.05. The ORs of these models were compared with the ORs of the models including all variables to identify confounding by an eliminated variable, with inclusion of this variable in cases of confounding. Current users of ICS or bronchodilators with a history of OAD before the index

date were compared with patients who had never been exposed to ICS or bronchodilators and who did not have a diagnosis of OAD.

Results

The study population included 108,754 adult patients who sustained an osteoporotic fracture (44,201 radius/ulna, 22,250 femur/hip, 16,189 rib, 14,646 humerus, 8,712 vertebral and 3,908 clavicle fractures). Baseline characteristics are listed in Table 3.2.1. The median time of enrolment before the index date was 2.2 years. In the overall study population, higher BMI (>25) was associated with a reduced risk of a hip fracture (crude OR 0.61 [95% confidence interval (CI) 0.56-0.66]), compared with patients with a BMI ranging 20-25. For patients with low BMI (<20), the reverse was observed (crude OR 1.78 [95% CI 1.58- 2.00]). Oral corticosteroid use was also associated with an increased risk of hip fracture (crude OR 1.75 [95% CI 1.58-1.95]).

Table 3.2.1 Baseline characteristics.

Characteristics	Cases (n=108,754)	(%)	Controls (n=108,754)	(%)
Age (years)				
Mean	62.3		62.3	
Median	66.7		66.8	
Females	71,828	66%	71,828	66%
Disease history before the index date				
Asthma	9,172	8.4%	6,737	6.2%
COPD	5,537	5.1%	3,463	3.2%
Acute bronchitis	3,190	2.9%	2,237	2.1%
Heart failure	7,586	7.0%	6,339	5.8%
Symptoms 1 year before the index date				
Exacerbations	1,174	1.1%	605	0.6%
Difficulty with breathing	3,326	3.1%	2,517	2.3%
Wheezing	1,018	0.9%	822	0.8%
Coughing	8,417	7.7%	6,554	6.0%
Respiratory infection	1,200	1.1%	956	0.9%
Drug use 6 months before the index date				
One or more bronchodilators	8,213	7.6%	5,745	5.3%
Short-acting beta-2 agonists	6,694	6.2%	4,626	4.3%
Inhaled anticholinergics	1,439	1.3%	829	0.8%
Xanthines	1,863	1.7%	1,237	1.1%
Long-acting beta-2 agonists	585	0.5%	335	0.3%
Inhaled corticosteroids	5,960	5.5%	4,107	3.8%
Oral corticosteroids	5,405	5.0%	2,989	2.7%
Body mass index				
<20	6,769	6.2%	4,875	4.5%
20-25	29,088	26.7%	25,949	23.9%
>25	28,354	26.1%	29,550	27.2%
Not determined	44,543	41.0%	48,380	44.5%

Of the cases with current oral corticosteroid use, 54% received five or more oral corticosteroid prescriptions in the previous year (for controls, this was 43%). The percentage of patients with continuous oral corticosteroid use for >six months was 44% among the cases and 36% among the controls (continuous use was defined as receiving a repeat oral corticosteroid prescription within three months of the previous prescription).

The risk of osteoporotic fracture was increased in patients with asthma (crude OR 1.28 [95% CI 1.23-1.32]), in patients with COPD (crude OR 1.61 [95% CI 1.52-1.71]), and in patients who had both diagnoses recorded (crude OR 1.72 [95% CI 1.60- 1.85]). Patients with an indicator of more severe OAD generally had increased risks of fracture (Figure 3.2.1) compared with patients without the indicator who did not have a history of OAD. For example, the risk of osteoporotic fracture among patients with OAD exacerbations was 2.02 [95% CI 1.82-2.23] and 2.54 [95% CI 1.90-3.40] among patients with a BMI <20. Patients with OAD who also smoked had an increased risk of osteoporotic fracture (crude OR 1.57 [95% CI 1.49-1.67]). Those who smoked <20 cigarettes/day had a crude OR of 1.57 [95% CI 1.41-1.76] compared with an OR of 1.79 [95% CI 1.24-2.57] in patients with OAD who smoked >20 cigarettes/day. Among patients with a history of OAD, the risk of osteoporotic fracture was increased in both current (crude OR 1.53; 95% CI 1.46-1.59) and past users (crude OR 1.36; 95% CI 1.27-1.47) of ICS, compared with those who had never used ICS and were not diagnosed with OAD.

Among the current users, the risk of fracture increased with daily dose (Table 3.2.2). Patients exposed to bronchodilators also had an increased risk of fracture. When the current authors adjusted for general risk factors, bronchodilator use and indicators of disease severity, current use of ICS was no longer associated with an increased risk of osteoporotic fracture (adjusted OR 1.04 [95% CI 0.97-1.11]). Furthermore, the dose response with ICS observed in the crude analysis was no longer statistically significant. Current users of beclomethasone, budesonide or fluticasone had a comparable risk of fracture. Most current users of ICS were also concomitantly exposed to bronchodilators (76% for cases and 72% for controls).

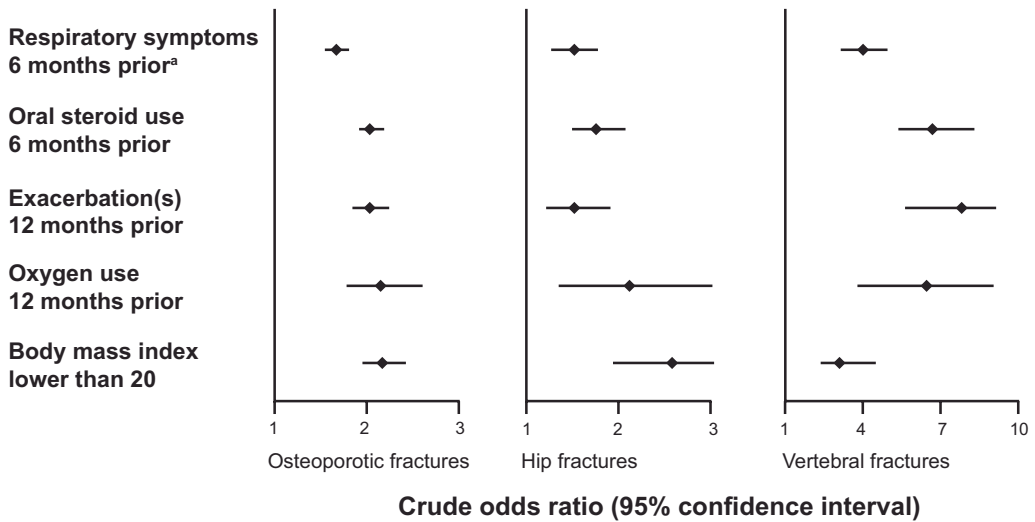


Figure 3.2.1 Crude odds ratios (95% confidence interval) for fracture among patients with obstructive airway disease. a: Respiratory symptoms included bacterial respiratory tract infections, coughing, presence of sputum, haemoptysis, dyspnoea, tachypnoea, shortness of breath, acute bronchitis and wheezing.

Table 3.2.2 Crude and adjusted odds ratios (OR) for fracture and use of inhaled corticosteroids and bronchodilators six months before the index date.

Fracture type and average daily dose	Inhaled corticosteroids				Bronchodilators			
	Crude		Adjusted	OR (95% CI) ^a	Crude		Adjusted	OR (95% CI) ^a
	Cases	Controls			Cases	Controls		
Referent			1.00	1.00			1.00	1.00
Osteoporotic	108,754	108,754						
<400 µg	1,747	1,211	1.41 (1.31–1.53)	1.04 (0.95–1.14)	1,650	1,183	1.37 (1.27–1.48)	1.20 (1.09–1.31)
401–800 µg	1,571	1,050	1.49 (1.37–1.62)	1.03 (0.93–1.14)	1,606	976	1.70 (1.57–1.85)	1.45 (1.32–1.60)
801–1,600 µg	1,367	788	1.77 (1.61–1.93)	1.15 (1.03–1.29)	1,642	1,091	1.57 (1.45–1.70)	1.28 (1.16–1.41)
>1,600 µg	512	281	1.95 (1.68–2.27)	1.19 (1.01–1.41)	1,375	817	1.81 (1.66–1.98)	1.35 (1.21–1.51)
Hip	14,388	14,388						
<400 µg	188	139	1.36 (1.08–1.71)	1.01 (0.76–1.34)	203	157	1.29 (1.04–1.61)	1.20 (0.94–1.55)
401–800 µg	212	164	1.29 (1.04–1.59)	0.97 (0.74–1.28)	257	153	1.75 (1.42–2.16)	1.58 (1.22–2.04)
801–1,600 µg	190	120	1.55 (1.22–1.97)	1.09 (0.81–1.48)	247	211	1.27 (1.05–1.53)	1.17 (0.91–1.50)
>1,600 µg	73	45	1.78 (1.21–2.62)	1.18 (0.75–1.85)	214	133	1.72 (1.37–2.16)	1.37 (1.01–1.86)
Vertebral	8,712	8,712						
<400 µg	205	84	2.61 (2.00–3.39)	1.60 (1.14–2.24)	168	101	1.80 (1.39–2.32)	1.03 (0.75–1.43)
401–800 µg	209	85	2.71 (2.07–3.55)	1.33 (0.93–1.90)	199	84	2.72 (2.08–3.57)	1.32 (0.94–1.86)
801–1,600 µg	209	87	2.88 (2.21–3.77)	1.21 (0.83–1.75)	228	88	3.00 (2.32–3.89)	1.43 (1.01–2.03)
>1,600 µg	101	20	6.11 (3.73–10.01)	1.85 (1.01–3.38)	269	79	4.15 (3.19–5.41)	1.62 (1.11–2.36)

a: Adjustments were made for general risk factors, smoking status, body mass index, duration of enrolment in the General Practice Research Database, indicators of OAD severity, and exposure to bronchodilators (inhaled corticosteroid group) or ICS (bronchodilator group).

Referent crude OR: subjects who were never exposed to ICS and who did not have a history of obstructive airway disease (OAD); referent adjusted OR: subjects who were never exposed to ICS and bronchodilators, and who did not have a history of OAD.

No statistically significant differences could be detected between the use of both drugs at the same time and single use. In the high-dose group ($>1,600$ μg beclomethasone equivalents per day), approximately half had not been exposed to oral corticosteroids in the previous six months. These patients did not have an increased risk of osteoporotic fracture (adjusted OR 1.19 [95% CI 0.96-1.47]). The risk of fracture was increased in patients who were exposed to both oral corticosteroids and high-dose ICS. For osteoporotic fracture, the adjusted OR was 1.79 (95% CI 1.40-2.29), for hip fracture 1.77 [95% CI 0.91-3.46], and 3.78 [95% CI 1.79-7.97] for vertebral fracture. The median number of prior oral corticosteroid prescriptions was 14 in these patients.

As shown in Table 3.2.3, patients with more severe OAD had higher risks of fracture, and these risks were comparable between users and nonusers of ICS. The adjusted OR for osteoporotic fracture was 1.47 [95% CI 1.25-1.74] in nonusers and 1.48 [95% CI 1.29-1.71] in users of ICS with more severe OAD.

Discussion

In the current study, the association between exposure to high doses of ICS and the risk of osteoporotic fracture was confirmed. Nevertheless, it was also found that the risk of fracture was related to indicators of severe OAD, and that patients using higher doses of bronchodilators also had increased risks of fracture. After adjustment for disease severity and use of bronchodilators, the initial association between use of ICS and risk of osteoporotic fracture almost disappeared.

Table 3.2.3 Association between obstructive airway disease (OAD) and risk of osteoporotic fracture stratified by presence of indicators of disease severity and use of inhaled corticosteroids six months before the index date.

Patients with OAD		Osteoporotic			Hip			Vertebral		
Severe OAD ^a	Use of inhaled corticosteroids	Crude	Adjusted		Crude	Adjusted		Crude	Adjusted	
		OR	OR (95% CI) ^b		OR	OR (95% CI) ^b		OR	OR (95% CI) ^b	
No	No	1.25	1.06 (0.92–1.22)		1.28	1.07 (0.67–1.70)		1.33	0.74 (0.44–1.22)	
No	Yes	1.32	1.08 (0.95–1.23)		1.26	1.08 (0.71–1.66)		1.67	1.01 (0.64–1.58)	
Yes	No	1.84	1.47 (1.25–1.74)		1.82	1.43 (0.87–2.35)		3.43	1.83 (1.03–3.23)	
Yes	Yes	1.92	1.48 (1.29–1.71)		1.61	1.37 (0.87–2.15)		4.69	2.57 (1.58–4.19)	

a: Severe disease was defined as the presence of one or more disease severity indicators (exacerbation of OAD, use of oxygen in the previous 12 months, use of oral corticosteroids, body mass index <20 , bacterial respiratory tract infections, coughing, presence of sputum, haemoptysis, dyspnoea, tachypnoea, shortness of breath, acute bronchitis and wheezing in the previous six months).

b: Adjusted for general risk factors, smoking status, duration of enrolment in the General Practice Research Database and exposure to bronchodilators.

Referent crude odds ratio (OR): subjects who were never exposed to inhaled corticosteroids and who did not have a history of OAD; referent adjusted OR: subjects who had never been exposed to inhaled corticosteroids and bronchodilators and who did not have a history of OAD; CI: confidence interval.

Two other studies, one using a case-control design and the other a cohort design, evaluated the risk of fracture of patients using ICS in GPRD.^{4,5} Both these studies found a dose-dependent increase in fracture risk, but they differed in their interpretation on the aetiology of this increased risk. The current authors were able to confirm the results of the case-control study⁵ when the same definitions were applied (i.e. timing of prior use of ICS was ignored by combining current and past users, and no adjustment was made for general risk factors, prior use of bronchodilators or disease-severity indicators, with the exception of oral corticosteroid use). However, when adjusting for disease-severity indicators, the hip fracture risk in patients using ICS was statistically comparable with nonusers, even at the higher doses. The present findings suggest an important role of the underlying respiratory disease in the aetiology of increased fracture risk.

There have been several studies that have evaluated the risk of fracture in users of ICS. A case-control study conducted in Denmark found a non-significant trend between use of high-dose inhaled and intranasal corticosteroids and risk of hip fracture, but the authors did not adjust for co-medication and severity indicators.⁷ In a nested case-control study among elderly American veterans with COPD, a dose-response relationship between short-term use of ICS and non-vertebral fracture risk was found. Adjustment for disease severity was limited to use of oral corticosteroids, the number of hospitalisations and the number of outpatient visits.⁶ The importance of adjustment for the underlying disease severity was confirmed in a nested case-control study conducted in a Canadian population. Hip fracture risk was not associated with exposure to high-dose ICS over a four-year period. The analysis was adjusted for the number of dispensings of bronchodilators.¹¹ In a cohort study consisting of Canadian females, exposure to ICS was not associated with an increased risk of hip fracture. Results were adjusted for a wide range of underlying diseases, including a history of COPD.¹⁰

The relationship between the use of ICS and BMD was analysed in two meta-analyses, with inconsistent results. A Cochrane review of randomised clinical trials found no evidence for an effect of ICS exposure on BMD; however, the patient population included in the randomised trials had relatively mild respiratory disease and was young.²² A meta-analysis, which also included observational studies, found that ICS users had, on average, a lower BMD than expected for their age and sex. To address the effect of confounding by underlying disease severity, Richy and co-workers classified studies on the basis of the type of controls to the ICS us-

ers: healthy population controls or controls with lung disease. It was found that ICS users had lower BMD in both sets of study populations and that these results were statistically similar. Nevertheless, the number of patients in the studies with healthy controls was quite small. Moreover, the largest differences between ICS users and controls were seen in the studies with healthy controls, although this was not statistically significant. In conclusion, this trend is consistent with the current hypothesis that underlying disease severity is important in the aetiology of reduced BMD in patients using ICS.²³

The severity of pulmonary disease inversely correlated with BMD in three studies. An analysis of the Third National Health and Nutrition Examination Survey (NHANES) revealed that the risk of osteoporosis among males and females was inversely correlated with the degree of their airway obstruction. Adjustment for age, smoking, BMI, physical activity and different types of medication (among others, inhaled or oral corticosteroids, bronchodilators and estrogens) did not change these results.¹³ In a group of elderly Japanese females with COPD who were not exposed to oral corticosteroids, the prevalence of osteoporosis was 50%, twice as high as a comparison group consisting of females of the same age with asthma.²⁴ A cross-sectional study in a general-practice setting among British females aged 45-76 years also showed an inverse relationship between forced expiratory volume in one second and BMD at the hip, which remained after adjustment for body weight and length. Although use of ICS was not measured, the results remained similar after exclusion of patients who had a history of respiratory disease.¹²

Several mechanisms have been suggested for this possible relationship between OAD and increased risk of fracture or osteoporosis. They include lack of physical activity,^{25,26} low BMI among patients with COPD,²⁷ smoking,²⁸ a decreased exposure to sunlight,¹³ decreased testosterone levels,²⁹ hypercapnia,³⁰ and chronic inflammation. Cytokines that are expressed in inflammatory diseases, such as asthma and/or COPD, include tumour necrosis factor (TNF)-alpha, transforming growth factor-beta, interleukin (IL)-1beta, IL-4 and IL-8. These cytokines have been shown to affect bone remodelling in vivo and in vitro.³¹⁻³⁷ However, it is uncertain whether these cytokine levels are also increased in the osteoblasts and osteoclasts at the basic multicellular unit³⁸ in humans with respiratory disease. In a study among 68 post-menopausal females with osteoporosis, a correlation between levels of plasma IL-8 or TNF-alpha and BMD was not found.³⁹ Many patients with OAD use beta-2 agonists. The adrenergic pathway may play a role

in the regulation of bone formation in ovariectomised mice.⁴⁰ The current authors stratified the bronchodilator group to beta-2 agonists, antimuscarinics, xanthines, cromones and adrenoceptor agonists (e.g. ephedrine), and were unable to find a clear relationship between any class of drugs and risk of fractures. An interesting finding in the present study was an increased risk of fracture among past users of inhaled corticosteroids. This might be related to a history of concomitant oral-steroid use or a history of OAD.

This study has several limitations. Data on physical activity and smoking were limited. It is not obligatory for participating practices to record smoking status. The current data on smoking were incomplete, and the present results on the relationship between smoking and risk of fracture were lower than those recently reported in a meta-analysis.⁴¹ There were no data on the loss of fat-free mass. Loss of fat-free mass has been associated with reduced BMD and more severe COPD, and might be a more concise marker of severity of OAD compared with BMI.^{42,43} Although the current authors did not have data on BMI for all patients, the present finding of an inverse relationship between BMI and fracture risk was consistent with those previously reported.^{44,45} Controlling for severity of the underlying disease could also be improved with spirometry data, which were not available in this study. Lastly, among the patients who used $\geq 1,600$ μg beclomethasone equivalents per day, a large number (46%) were using oral corticosteroids (median number of oral-corticosteroid prescriptions was 14). Therefore, it may be difficult in this patient group to separate the effects of oral corticosteroids and ICS.

In conclusion, patients using higher doses of ICS have an increased risk of osteoporotic fracture. However, patients using bronchodilators and those with more severe obstructive airway disease also have an increased risk of fracture, and the dose-response relationship between ICS and fracture risk almost disappears after adjustment for disease severity. Consequently, adequate adjustment for disease severity is essential when the association between use of ICS and risk of fracture is studied in observational research.

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Chapter 3.3

Use of Inhaled and Oral Corticosteroids, Severity of Inflammatory Disease and Risk of Hip/Femur Fracture: a Population-Based Case-Control Study

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Summary

Background. Patients using higher dosages of inhaled corticosteroids (ICS) or oral corticosteroids (OCs) have an increased risk of hip/femur fractures. The role of the underlying disease in the aetiology of this increased risk has not been widely studied.

Objective. To evaluate the contribution of the underlying disease to the risk of hip/femur fracture in patients using ICS or OCs

Design and subjects. A case-control study within the Dutch PHARMO RLS database was conducted. Cases (n=6,763) were adult patients with a first hip/femur fracture during enrolment. Each case was matched to four controls by age, gender and region.

Results. The risk of hip/femur fracture increased with current use of ICS (crude OR 1.30 [95% CI 1.16-1.47]) and with current use of OCs (crude OR 1.66 [95% CI 1.46-1.90]). After adjustment for disease severity, the risk of hip/femur fracture was no longer statistically significantly increased in ICS users (adjusted OR 1.08 [95% CI 0.91-1.27]), while it remained elevated in OC users (adjusted OR 1.43 [95% CI 1.22-1.67]). Patients using ICS without any exposure to OCs had no increased risk of fracture (adjusted OR 0.98 [95% CI 0.79-1.22]).

Conclusion. ICS users had no increased risk of hip/femur fracture after adjustment for underlying disease severity. Our data suggest that, even at higher dosages, ICS use is not an independent risk factor for fracture. In contrast, OC use was associated with an increased risk of fracture, which was not fully explained by the underlying disease severity.

Introduction

Oral corticosteroids (OCs) and inhaled corticosteroids (ICS) are frequently prescribed to patients with inflammatory disease such as obstructive airway disease, rheumatoid arthritis (RA) or inflammatory bowel disease (IBD).^{1,2} Use of OCs has been found to decrease bone mineral density and increase the risk of fracture.^{3,4} These increases in the risk of fracture correlate with the daily dose of OCs.^{5,6} For ICS decreases in bone mineral density and increases in the risk of fracture have also been reported.

However, there has been controversy about the aetiology of these increases in the risk of fracture in users of ICS.⁷⁻¹⁰ Although these medications are administered locally, they undergo systemic absorption at higher dosages and may induce a suppression of plasma cortisol.¹¹ This may lead to low bone mineral density and increased risk of fracture. An alternative explanation for these effects on the bone may be the underlying obstructive airway disease.¹²⁻¹⁵ A reanalysis of a study conducted in the United Kingdom (UK) with the General Practice Research Database (GPRD) found that a previously reported dose-response association between ICS use and risk of fracture disappeared after adjustment for the severity of obstructive airways disease.^{7,16} The aim of this study was to evaluate the possible contribution of the underlying disease to the risk of hip/femur fracture in patients using ICS or OCs in a different population.

Methods

Study design

PHARMO RLS (www.pharmo.nl) is a database that contains the pharmacy dispensing data for a population of about one million Dutch patients. These dispensing data are linked to a nationwide hospital discharge register.¹⁷ In the Netherlands, pharmacies maintain a virtually complete register of dispensed medications, which have been prescribed by specialists and general practitioners. Patients are included irrespective of their health insurance or socioeconomic status, and represent about 7% of the general population. Several independent validation studies have shown that the PHARMO RLS database has a high level of completeness and validity.^{18,19}

Cases and control subjects

Within PHARMO RLS, a case-control study was conducted. Cases were patients who were 18 years or older and who sustained a hip/femur fracture during the study period (1 January 1991 to 31 December 2002). Each case was matched to up to four control patients (PHARMO RLS participants without any fracture during enrolment) by year of birth, gender and region. The date of the first hip/femur fracture was defined as the index date. Each control was assigned the index date of the matched case.

Exposure assessment

Current exposure was defined as the dispensing of at least one OC (predniso(lo)ne, dexamethsone, triamcinolone, hydrocortisone) or ICS (fluticasone, beclomethasone, budesonide) in the four months before the index date, because Dutch health insurance policies cover the dispensing of the majority of drugs for periods of three months. Past users were patients who received their last OC dispensing more than four months before the index date. For each current user, the cumulative exposure was calculated by summing the total amount of dispensings between enrollment in PHARMO RLS and the index date. The average daily dose was calculated by dividing the cumulative exposure by the total treatment time. Using defined daily dosages, exposure was expressed as oral prednisone equivalents or inhaled beclomethasone equivalents.²⁰

Covariate assessment

For the ICS analyses, we measured indicators of respiratory disease severity within six or 12 months before the index date, similar to previous studies.^{16,21,22} These included asthma/Chronic Obstructive Pulmonary Disease (COPD) exacerbations and the use of inhaled anticholinergics, beta-2 agonists, OCs, xanthine derivatives, acetylcystein, in the six months before the index date. Dispensings of antibiotics within $\pm$ three days before or after an OC dispensing were considered an asthma/COPD exacerbation.²³ Hospitalisations for asthma/ COPD in the one-year before the index date and administration of nebulised respiratory medications in the six months before were also measured. Likewise, for the OC analyses, we determined indicators of inflammatory disease. These included the respiratory disease severity indicators, exposure to DMARDs (methotrexate, azathioprine, mesasalazin, salazopyrin, gold preparations, and penicillamin within six months before the index date in order to estimate prevalent disease), and a history of hospitalisations for inflammatory bowel disease (IBD) or rheumatoid arthritis (RA)/Polymyalgia Rheumatica/Bechterew's disease. The following

general potential confounding factors were also determined: use of benzodiazepines within three months prior to the index date (under Dutch law, most benzodiazepines can not be prescribed for longer than 30 days), use of antipsychotics, antidepressants, anticonvulsants, antidiabetic agents, beta-blockers, hormone replacement therapy and ≥ 2 dispensings for a non-steroidal anti-inflammatory drug (NSAID) within the six months before index date and a history of hospitalisations for anemia, mental disorders, endocrine disorders and cerebrovascular disease before index date.

Statistical analysis

Conditional logistic regression was used to estimate odds ratios (OR) for hip/femur fracture (SAS version 9.1.3, PHREG procedure). Two different adjustments were made in the regression analyses. The first analysis adjusted for indicators of the severity of the underlying respiratory disease (ICS analysis), or inflammatory disease (OC analysis). The second analysis adjusted not only for disease severity indicators but also for general risk factors of hip/femur fracture. Backward selection of variables was used in the regression analyses. We also used smoothing spline regression plots (SAS version 9.1.3) to visualise the longitudinal relationship of risk of fracture with time between the index date and last dispensing of OCs (recency of use), and cumulative OC exposure.²⁴

Results

We identified 6,763 patients who suffered a hip/femur fracture. These cases were matched to 26,341 controls. The mean age was 75 years and 73% of the case patients were female. The majority of hip fractures (93%) occurred among subjects who were 50 years or older (Table 3.3.1). The mean period of time with prescription information prior to the index date was 4.1 years.

Indicators for the severity of the respiratory or inflammatory disease were associated with increased risk of hip/femur fracture. Hospitalisations for asthma/COPD in the one-year prior to the index date doubled the risk of hip/femur fracture (crude OR 2.17 [95% confidence interval (CI) 1.41-3.34]). In addition, asthma/COPD exacerbations and the use of nebulised medications six months before the index date increased the risk of hip/femur fractures (crude ORs 1.67 [95% CI 1.29-2.17] and 2.35 [95% CI 1.39-3.96], respectively. Hospitalisations for IBD (crude OR 1.58 [95% CI 1.39-1.79]) and RA/Polymyalgia Rheumatica/Bechterew's

Table 3.3.1 Baseline characteristics.

Characteristic	Cases (n=6,763)	(%)	Controls (n=26,341)	(%)	Crude OR (95% CI)
Mean age (years)	75.7		75.3		
Number females, %	4,929	73%	19,138	73%	
Use 6 months before the index date					
Short acting beta-2 agonists	388	6%	1,100	4%	1.41 (1.25-1.59)
Long acting beta-2 agonists	148	2%	488	2%	1.21 (1.00-1.46)
Anticholinergics	323	5%	1,002	4%	1.27 (1.12-1.45)
Xanthine derivatives	131	2%	281	1%	1.85 (1.50-2.29)
N-Acetylcystein	278	4%	803	3%	1.37 (1.19-1.57)
Inhaled corticosteroids	437	6%	1,316	5%	1.32 (1.18-1.48)
Oral corticosteroids	366	5%	918	3%	1.59 (1.40-1.80)
DMARDs	115	2%	202	1%	2.27 (1.80-2.86)
Hospitalisation before index date					
Cardiovascular disease	359	5%	1,289	5%	1.10 (0.98-1.25)
Cerebrovascular disease	296	4%	565	2%	2.12 (1.84-2.45)
RA/Polymyalgia Rheumatica/ Bechterew's disease	245	4%	731	3%	1.34 (1.16-1.56)

disease (crude OR 1.34 [95% CI 1.16-1.56]) were also associated with an increased risk of hip/femur fracture.

As shown in Table 3.3.2, the risk of hip/femur fracture increased with current use of ICS (crude OR 1.30 [95% CI 1.16-1.47]) and with current use of OCs (crude OR 1.66 [95% CI 1.46-1.90]) (Table 3.3.3). After adjustment for indicators of severity of the underlying respiratory disease, the risk of hip/femur fracture was no longer statistically significantly increased with current use of ICS (adjusted OR 1.08 [95% CI 0.91-1.27]). In contrast, the risk of hip/femur fracture remained statistically significantly increased with use of OCs after additional adjustment for indicators of disease severity (adjusted OR 1.43 [95% CI 1.22-1.67]).

For current users of higher daily dosages of ICS, similar findings were demonstrated ($\geq 1,600$ μg /day: crude OR 2.02 [95% CI 1.24-3.29]) or OCs (≥ 15 mg/day: crude OR 2.09 [95% CI 1.42-3.07]). The excess risk of hip/femur fracture substantially decreased after adjustment for indicators of underlying respiratory disease severity in ICS users, and was no longer significantly increased compared to non-users (adjusted OR 1.43 [95% CI 0.85-2.41]). In contrast, adjustment for indicators of disease severity did not substantially change the risk of hip/femur fracture in high dose OC users (adjusted OR 1.87 [95% CI 1.26-2.78]).

There was no association between the time since the last dispensing of an ICS and risk of hip/femur fracture (Figure 3.3.1). Conversely, current OC users had an increased risk of hip/femur fractures, which slowly decreased to baseline after discontinuation of OCs (Figure 3.3.2).

Table 3.3.2 Use of inhaled corticosteroids (ICS) and risk of hip/femur fracture.

ICS use before	Cases (n=6,763)	(%)	Controls (n=26,341)	(%)	Crude OR (95% CI)	Adjusted OR (95% CI) ^b	Adjusted OR (95% CI) ^c
Never use	6,047	89.4%	24,021	91.2%	1.00	1.00	1.00
Past use	334	4.9%	1,145	4.3%	1.17 (1.03-1.32)	1.08 (0.95-1.24)	1.02 (0.89-1.17)
Current use	382	5.6%	1,175	4.5%	1.30 (1.16-1.47)	1.08 (0.91-1.27)	1.07 (0.91-1.27)
Average daily dose ^a							
≤ 400 µg	94	1.4%	315	1.2%	1.19 (0.94-1.50)	1.04 (0.81-1.34)	1.03 (0.79-1.33)
401-800 µg	124	1.8%	409	1.6%	1.23 (1.00-1.50)	1.04 (0.82-1.31)	1.04 (0.82-1.32)
801-1,600 µg	109	1.6%	300	1.1%	1.47 (1.17-1.83)	1.17 (0.89-1.53)	1.14 (0.87-1.50)
≥ 1,600 µg	26	0.4%	49	0.2%	2.02 (1.24-3.29)	1.43 (0.85-2.41)	1.51 (0.89-2.54)
Not classified ^d	29	0.4%	102	0.4%	1.15 (0.76-1.75)	1.04 (0.68-1.59)	1.07 (0.69-1.64)

a: Average daily dose: cumulative exposure divided by the treatment time (µg inhaled beclomethasone equivalents).

b: Adjusted for indicators of underlying respiratory disease severity (i.e. use of short or long acting beta-2 agonists, inhaled anticholinergics, xanthines, acetylcystein, average daily dose of OCs, use of nebulised medications, ≥ 1 exacerbations, and ≥ 1 asthma/COPD hospitalisations).

c: Adjusted for indicators of the underlying respiratory disease severity (listed under b) and general risk factors for fracture (i.e. use of benzodiazepines, hormone replacement therapy, antipsychotics, antidepressants, beta-blockers, anticonvulsants, antidiabetics, two or more NSAID dispensings, disease modifying anti rheumatic drugs, anemia, mental disorders, cerebrovascular disease, heart failure, endocrine disorders and IBD).

d: Not classified: average daily dose could not be determined for current ICS users with one prescription.

Table 3.3.3 Use of oral corticosteroids (OCs) and risk of hip/femur fracture.

OC use before	Cases (n=6,763)	(%)	Controls (n=26,341)	(%)	Crude OR (95% CI)	Adjusted OR (95% CI) ^b	Adjusted OR (95% CI) ^c
Never use	5,941	87.9%	24,026	91.2%	1.00	1.00	1.00
Past use	500	7.3%	1,527	5.8%	1.34 (1.20-1.49)	1.25 (1.11-1.40)	1.18 (1.05-1.32)
Current use	322	4.7%	788	3.0%	1.66 (1.46-1.90)	1.43 (1.22-1.67)	1.32 (1.13-1.55)
Average daily dose ^a							
< 7.5 mg	153	2.3%	405	1.5%	1.54 (1.28-1.86)	1.31 (1.05-1.63)	1.23 (0.98-1.54)
7.5-15.0 mg	87	1.3%	154	0.6%	2.30 (1.76-3.00)	1.98 (1.50-2.62)	1.76 (1.32-2.34)
≥ 15.0 mg	40	0.6%	77	0.3%	2.09 (1.42-3.07)	1.87 (1.26-2.78)	1.69 (1.13-2.53)
Not classified ^d	42	0.6%	152	0.6%	1.12 (0.80-1.58)	1.00 (0.70-1.41)	0.95 (0.67-1.36)

a: Average daily dose: cumulative exposure divided by the treatment time (mg prednisone equivalents).

b: Adjusted for indicators of underlying respiratory disease severity (i.e. use of short or long acting beta-2 agonists, inhaled anticholinergics, xanthines, acetylcystein, ICS, use of nebulised medications, ≥ 1 exacerbations, and ≥ 1 asthma/COPD hospitalisations), and other indicators of underlying inflammatory disease (i.e. use of methotrexate, azathioprine, mesasalazin, salazopyrin, gold preparations, and penicillamin, ≥ 1 IBD hospitalisations and ≥ 1 RA/Polymyalgia/Bechterew's disease hospitalisations).

c: Adjusted for indicators of the underlying respiratory and inflammatory disease severity (listed under b) and general risk factors for fracture (i.e. use of benzodiazepines, hormone replacement therapy, antipsychotics, antidepressants, beta-blockers, anticonvulsants, antidiabetics, two or more NSAID dispensings, anemia, mental disorders, cerebrovascular disease, heart failure, and endocrine disorders).

d: Not classified: average daily dose could not be determined for current OC users with one prescription.

Table 3.3.4 Average daily dose of current users of inhaled corticosteroids (ICS) and risk of hip/femur fracture by average daily OC dose in the four months before the index date.

Use of ICS	Current exposure to OCs		
	Average daily dose		
	Never Adjusted	<7.5 mg/day Adjusted	≥ 7.5 mg/day Adjusted
	OR (95% CI) ^a	OR (95% CI) ^a	OR (95% CI) ^a
Never exposed	1.00	1.29 (0.97-1.71)	1.57 (1.19-2.06)
Current exposure to ICS	0.98 (0.79-1.22)	1.05 (0.73-1.51)	1.25 (0.71-2.18)
Average daily dose			
ADD ≤ 400 µg	0.93 (0.67-1.31)	1.13 (0.57-2.23)	1.82 (0.60-5.54)
ADD 401-800 µg	1.05 (0.75-1.47)	0.92 (0.55-1.54)	0.95 (0.35-2.57)
ADD 801-1,600 µg	0.92 (0.59-1.43)	1.17 (0.68-2.02)	1.02 (0.39-2.68)
ADD ≥ 1,600 µg	1.29 (0.54-3.07)	1.15 (0.35-3.78)	1.70 (0.46-6.32)

a: See Table 3.3.3 (c) for adjustments for disease severity indicators and general risk factors, excluding exposure to OCs.

The association between cumulative exposure to inhaled and OCs and risk of hip/femur fractures is shown in Figures 3.3.3 and 3.3.4. The risk of hip/femur fracture was increased after exposure to >1 gram of OCs yielding an adjusted OR of 1.40 [95% CI 1.18-1.66].

Table 3.3.4 shows that the risk of femur/hip fracture in OC users was independent of concomitant use of ICS. The adjusted OR was 1.57 [95% CI 1.19-2.06] in patients who used OCs at a daily dose of 7.5 mg or more and who were never exposed to ICS. In those with current exposure to ICS, the adjusted OR was 1.25 [95% 0.71-2.18]. It was also found that users of ICS had a fracture risk comparable to controls at all daily dosages when excluding subjects who had been exposed to OCs before index date. The adjusted OR was 0.93 [95% CI 0.67-1.31] in ICS users with a daily dose of ≤400 µg, 1.05 [95% CI 0.75-1.46] with a daily dose of 401-800 µg, 0.92 [95% CI 0.60-1.43] with a daily dose of 801-1,600 µg and 1.29 [95% CI 0.53-3.04] with a daily dose of ≥1,600 µg beclomethasone equivalents).

Discussion

We found that current users of inhaled and OCs had increased risks of hip/femur fracture, especially at higher daily dosages. The excess risk among ICS users mostly disappeared after adjustment for respiratory disease severity, whereas the risk of hip/femur fracture remained statistically elevated in OC users after adjustment for inflammatory disease severity. Patients without a history of use of OCs use were not at increased hip/femur fracture risk at all daily dosages of ICS intake.

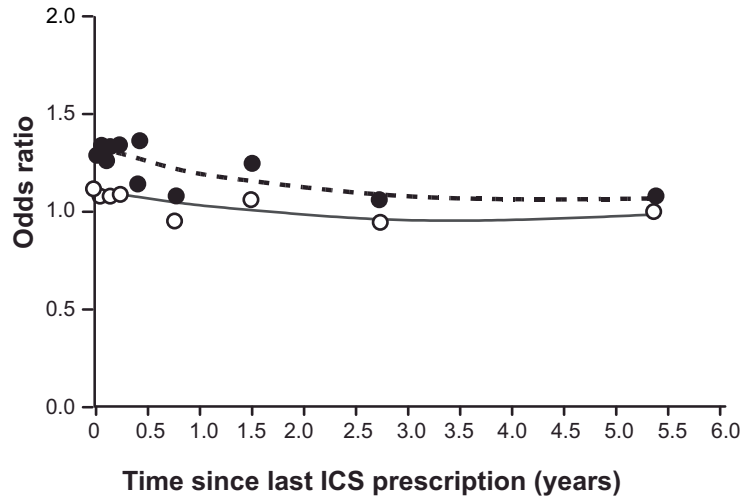


Figure 3.3.1 Time since last inhaled corticosteroid prescription and risk of hip/femur fracture. Dashed line, solid circles: crude odds ratios. Solid lines, open circles: fully adjusted (see Table 3.3.2, footnote c) odds ratios.

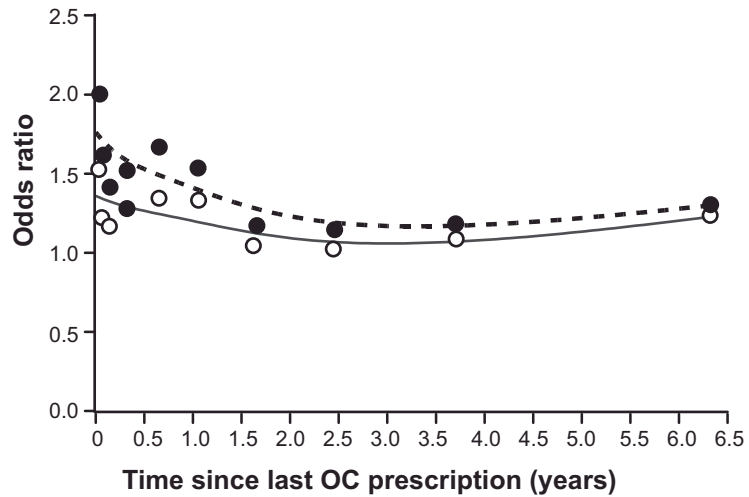


Figure 3.3.2 Time since last OC prescription and risk of hip/femur fracture. Dashed line, solid circles: crude odds ratios. Solid lines, open circles: fully adjusted (see Table 3.3.3, footnote c) odds ratios.

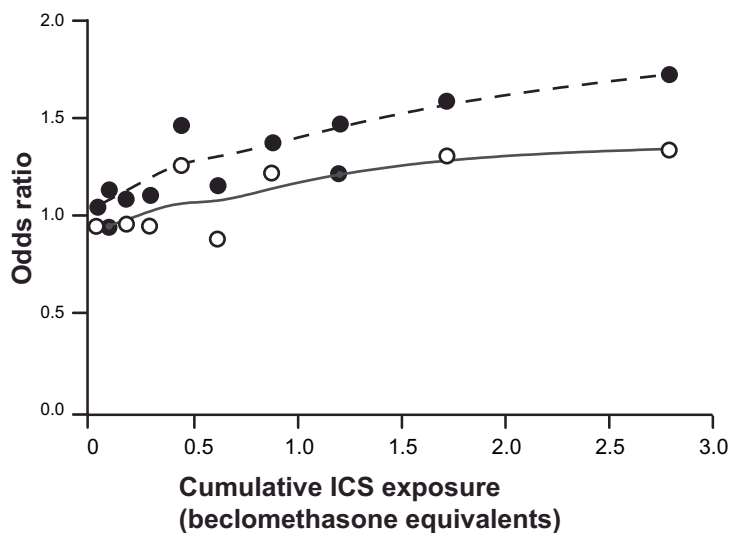


Figure 3.3.3 Cumulative exposure to inhaled corticosteroids (ICS) among current users and risk of hip/femur fracture. Dashed line, solid circles: crude odds ratios. Solid lines, open circles: fully adjusted (see Table 3.3.2, footnote c) odds ratios.

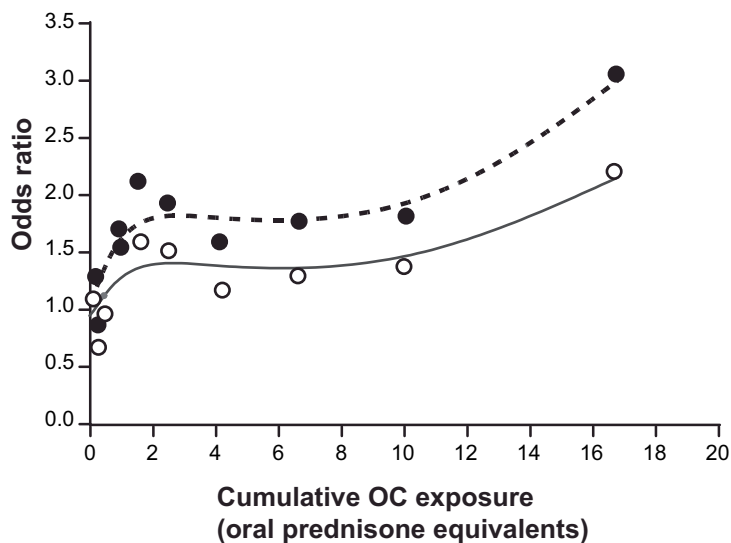


Figure 3.3.4 Cumulative exposure to oral corticosteroids (OCs) among current users and risk of hip/femur fracture. Dashed line, solid circles: crude odds ratios. Solid lines, open circles: fully adjusted (see Table 3.3.3, footnote c) odds ratios.

Our results of the crude risk of hip/femur fracture in ICS users are consistent with previous large epidemiological studies.^{9,16} We clearly showed that patients using higher daily dosages of ICS had increased risks of hip/femur fracture. Several epidemiological studies have also reported reduced bone mineral density or increased hip fracture risk in patients using ICS.^{7,8,25} However, none of these studies extensively adjusted for the severity of the underlying respiratory disease.^{12,13} We found that the excess fracture risk in ICS users decreased substantially after adjustment for disease severity. This is in line with the results from a study in the United Kingdom (UK) that reported different results with and without adjustment for respiratory disease severity.^{7,16} These findings are supported by the observations in two studies that lung function and bone mineral density were inversely correlated, independent of OC use.^{14,15}

Our results suggest an increased risk of hip/femur fracture in OC users and this is consistent with previous observational studies.^{5,6,26} Our finding of a reduction in hip/femur fracture risk towards baseline levels after discontinuation of OCs is similar to that of a large study from the UK.⁵ We also found that confounding by the underlying inflammatory disease played a small role in the association between OC use and risk of hip/femur fracture. Inflammatory diseases like RA and IBD have been associated with fracture risk regardless of OC use.^{27,28} However, a meta-analysis suggested that OC-induced fracture risk is at least partially related to OC therapy.³

Our study had a reasonable sample size to study the associations between OCs and risk of hip/femur fracture. It was population-based because drug dispensings were reimbursed regardless of socio-economic status or employment. Moreover, drug-dispensing data was routinely collected since 94% of Dutch patients collect their drug dispensings from the same pharmacy.²⁹

Limitations of this study included absence of data on body mass index, fat free mass, smoking status, exercise, or high-impact trauma.³⁰⁻³³ We could only control for more severe diagnoses that required an inpatient hospitalisation, as computerised registers of general practitioner were unavailable. Adjustments for the severity of the underlying disease included proxy indicators such as use of a wide range of respiratory medications, DMARDs and exacerbations. For example, we did not have specific data on the lung function, symptoms like diarrhoea or rectal bleeding. Given the reduced lung function in ICS users and the reported inverse association between lung function and bone mineral density,^{14,15} it is likely that better adjustment for respiratory disease severity would further de-

crease the small excess risk of hip/femur fracture in ICS users. Another limitation was that the statistical power was limited in the subgroup of high dose ICS user. However, our result of no association was consistent with those previously reported in the UK General Practice Research Database.¹⁶

In conclusion, ICS users had no increased risk of femur/hip fracture after adjustment for underlying disease severity. Our data suggest that, even at higher dosages, ICS use is not an independent risk factor for fracture. In contrast, OC use was associated with an increased risk of fracture, which was not fully explained by the underlying disease severity.

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Chapter 3.4

Use of Beta-2 Agonists and Risk of Hip/Femur Fracture: a Population-Based Case-Control Study

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Summary

Background. Administration of beta-2 agonists decreased bone mineral density in rats. But the association between bronchodilators and fracture risk has not been studied in humans.

Objective. To examine the association between use of beta-2 agonists and risk of hip/femur fracture.

Methods. We conducted a population-based case-control study (6,763 cases) in the Dutch PHARMO RLS database. Current beta-2 agonist use was compared to never use. We adjusted for severity of the underlying respiratory disease and disease and drug history.

Results. A hospitalisation for asthma/COPD in the year before index date increased risk of hip/femur fracture: crude OR 2.17 [95% CI [1.41-3.34]. Patients using higher doses of beta-2 agonists had increased risk of hip/femur fracture: crude OR 1.94 [95% CI 1.41-2.66] for daily dosages of $\geq 1,600$ μg salbutamol equivalent (salbutamol is a synonym of albuterol). The excess fracture risk reduced after adjustment for disease severity (1.46 [95% CI 1.02-2.08]) and after exclusion of oral corticosteroid users (1.31 [95% CI 0.80-2.15]. Risk of hip/femur fracture was similar between users of beta-2 agonists, inhaled corticosteroids (ICS) and inhaled anticholinergics.

Conclusion. We found increases in the risk of hip/femur fracture in patients using higher doses of beta-2 agonists. However, the excess risk of hip/femur fracture substantially reduced after exclusion of OC users and after adjustment for the underlying disease. Risk of hip/femur fracture was similar between users of beta-2 agonists, ICS and inhaled anticholinergics. The severity of the underlying disease, rather than the use of beta-2 agonists, may play an important role in the aetiology of hip/femur fractures in patients using beta-2 agonists.

Introduction

Beta-2 agonists are drugs that are frequently used in the treatment of asthma and chronic obstructive pulmonary disease (COPD). They have been designed to act on the beta-2 adrenergic receptor, causing smooth muscle relaxation resulting in dilation of bronchial passages. Beta-2 adrenergic receptors are also present at osteoblasts and can modulate bone remodeling.¹ Noradrenergic activation of the beta-2 receptor leads to production of RANK ligand by osteoblasts. RANK ligand stimulates the formation of osteoclasts, which ultimately leads to a decrease of bone mineral density.² Administration of beta-2 agonists decreased bone mineral density and strength in rats,³ whereas the beta-blocker propranolol had opposite effects.⁴

Orally administered beta-blockers have been associated in epidemiological studies with increased bone mineral density and decreased risk of fracture.⁵⁻⁷ Given these findings, it would be of interest to establish whether beta-2 agonists would have bone effects opposite to beta-blockers. Systemic cardiac effects and increases in plasma levels have been reported with inhalation of beta-2 agonists.⁸⁻¹⁰ A large population-based cohort study found an increased risk of fracture in patients using bronchodilators, but this study did not evaluate in detail the association between type of bronchodilator and risk of fracture.¹¹ Therefore, the aim of this study was to examine the association between use of beta-2 agonists and risk of hip/femur fracture.

Methods

Study design

PHARMO RLS (www.pharmo.nl) is a database that contains the pharmacy dispensing data for a population of about one million Dutch patients. These prescription data are linked to a nationwide hospital discharge register.¹² In the Netherlands, pharmacies maintain a virtually complete register of dispensed medications, which have been prescribed by specialists and general practitioners. Patients are included irrespective of their health insurance or socioeconomic status, and represent about 7% of the general population. Several independent validation studies have shown that the PHARMO RLS database has a high level of completeness and validity.^{12,13}

Cases and control subjects

Within PHARMO RLS, a case-control study was conducted. Cases were patients who were 18 years or older and who sustained a hip/femur fracture during the study period (1 January 1991-31 December 2002). Each case was matched to up to four control patients (PHARMO RLS participants without any fracture during enrolment) by year of birth, gender, and region. The date of the first hip/femur fracture was defined as the index date. Each control was assigned the index date of the matched case.

Exposure assessment

In Dutch pharmacies, respiratory medications are usually dispensed for three months use. Therefore, current exposure was defined as the dispensing of at least one short acting beta-2 agonist (salbutamol, fenoterol, terbutaline, -salbutamol is a synonym of albuterol-) or long acting beta-2 agonist (salmeterol, formoterol) in the four months before the index date. Past users were patients who received their last beta-2 agonist prescription more than four months before the index date. Cumulative exposure was calculated by summing the total amount of dispensed beta-2 agonists. The average daily dose was calculated by dividing the total cumulative dose by the total treatment time. We expressed dosages as salbutamol equivalents using defined daily dosages.¹⁴ We also measured indicators of severity of the underlying respiratory disease.¹⁵ This included exposure to inhaled anticholinergics, inhaled corticosteroids (ICS) and oral corticosteroids (OCs), xanthine derivatives, acetylcystein and antibiotics within 3 days before or after an OC prescription (a marker for an exacerbation¹⁶) six months prior to the index date. Moreover, hospitalisations for asthma/COPD in the one-year before the index date and nebulised administration of respiratory medications in the six months before were also included as indicators of underlying disease severity. History of diseases and prior use of drugs that previously have been identified as general risk factors for fracture were treated as potential confounders.^{17,18}

Conditional logistic regression was used to estimate odds ratios (OR) for fracture (SAS version 9.1.3, PHREG procedure). Two different adjustments were made in the regression analyses. The first analysis adjusted for indicators of the severity of the underlying disease. The second analysis adjusted not only for disease severity indicators but also for general risk factors. Backward selection of variables was used in the regression analyses. We also used smoothing spline regression plots (SAS version 9.1.3) to visualise the longitudinal relationship of risk of fracture with time between

the index date and last dispensing of beta-2 agonists (recency of use).¹⁹

Table 3.4.1 Characteristics of cases and controls.

Characteristic	Cases (n=6,763)		Controls (n=26,341)		Crude OR (95% CI)
Mean age (years)	75.7		75.3		
Number females, %	4,929	73%	19,138	73%	
Use 6 months before the index date					
Short acting beta-2 agonists	388	6%	1,100	4%	1.41 (1.25-1.59)
Long acting beta-2 agonists	148	2%	488	2%	1.21 (1.00-1.46)
Anticholinergics	323	5%	1,002	4%	1.27 (1.12-1.45)
Xanthine derivatives	131	2%	281	1%	1.85 (1.50-2.29)
N-Acetylcystein	278	4%	803	3%	1.37 (1.19-1.57)
ICS	437	6%	1,316	5%	1.32 (1.18-1.48)
OCs	366	5%	918	3%	1.59 (1.40-1.80)
Beta-blockers	957	14%	4,068	15%	0.91 (0.84-0.98)
Hospitalisation before index date					
Cardiovascular disease	359	5%	1,289	5%	1.10 (0.98-1.25)
Cerebrovascular disease	296	4%	565	2%	2.12 (1.84-2.45)
RA/Polymyalgia Rheumatica/ M. Bechterew	245	4%	731	3%	1.34 (1.16-1.56)

Results

We identified 6,763 patients who suffered hip/femur fracture. They were matched to 26,341 controls. The average age of cases was 75 years, and 73% were female (Table 3.4.1). The average time-period with prescribing data prior to the index date was 4.1 years (inter-quartile range 1.2-6.4 years). There were a total number of 41,740 prescriptions for bronchodilators: 26,204 (62.8%) for salbutamol, 2,123 (5.1%) for fenoterol, 3,921 (9.4%) for terbutaline, 6,598 (15.8%) for salmeterol and 2,882 (6.9%) for formoterol. Among current beta-2 agonist users, the average daily dose was 967 µg salbutamol equivalent for cases, and 829 µg salbutamol equivalent for controls. 6.0% of current beta-2 agonist users had been prescribed OCs with a daily dose ≥ 7.5 mg prednisolone equivalent in the six months prior to the index date.

Indicators of the severity of the respiratory disease were associated with increased risk of hip/femur fracture. If patients had been hospitalised for asthma/ COPD in the one-year before, the crude OR for hip/ femur fracture was 2.17 [95% confidence interval (CI), 1.41-3.34]. Prior use of OCs in the six months before was also associated with an increased risk of hip/femur fracture. At an average daily dose of <7.5 mg prednisolone equivalents, the crude OR was 1.41 [95% CI, 1.17-1.69], at 7.5-15 mg daily this OR was 2.23 [95% CI, 1.74-2.86], and at ≥ 15 mg daily this OR was 2.64 [95% CI, 1.85-3.77].

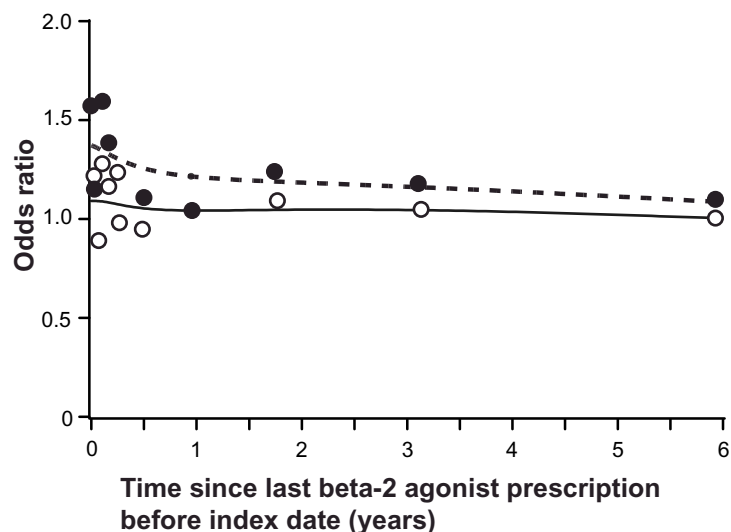


Figure 3.4.1 Recency of beta-2 agonist use before the index date and risk of hip/femur fracture. Dashed line and solid circles: crude ORs; solid line and open circles: adjusted ORs. Adjustments were made for the same indicators of severity of OAD and general risk factors as in Table 3.4.2, footnote c.

General risk factors that were associated with increased hip/femur fracture risk included use of benzodiazepines three months prior to the index date (OR 1.44 [95% CI 1.33-1.56], antipsychotics (OR 1.79 [95% CI 1.58-2.02], antidepressants (OR 2.00 [95% CI 1.81-2.21], anticonvulsants (OR 2.23 [95% CI 1.90-2.61]), antidiabetic agents (OR 1.37 [95% CI 1.25-1.49]), disease modifying anti-rheumatic drugs (DMARDs) (OR 2.27 [95% CI 1.80-2.86]), and ≥ 2 prescriptions for a non-steroidal anti-inflammatory agent (NSAID, OR 1.46 [95% CI 1.35-1.59]. In addition, a history of anaemia (OR 2.41 [95% CI 1.71-3.39]), mental disorders (OR 2.54 [95% CI 1.51-4.27]), endocrine disorders (OR 2.10 [95% CI 1.76-2.51]), cerebrovascular disease (OR 2.12 [95% CI 1.84-2.45]) and inflammatory bowel disease (OR 1.72 [95% CI 1.25-2.36]) were also associated with increased risk of hip/femur fracture. In contrast, hip/femur fracture risk was reduced in subjects who were treated with beta-blockers (OR 0.91 [95% CI 0.84-0.98]) six months before the index date.

Current exposure to beta-2 agonists increased risk of hip/femur fracture in the univariate analysis (OR 1.39 [95% CI 1.24-1.56], Table 3.4.2). After adjustment for indicators of severity of the underlying disease, use of beta-2 agonists was no longer associated with risk of fracture (OR 1.15 [95% CI 0.98-1.35]) Further

Table 3.4.2 Use of beta-2 agonists and risk of hip/femur fracture.

Beta-2 agonist use	Cases (n=6,763)	(%)	Controls (n=26,341)	(%)	Crude OR (95% CI)	Adjusted OR (95% CI) ^b	Adjusted OR (95% CI) ^c
Never use	5,926	87.6%	23,690	89.9%	1.00	1.00	1.00
Past use	395	5.8%	1,366	5.2%	1.16 (1.03-1.30)	1.10 (0.98-1.24)	1.03 (0.91-1.17)
Current use	442	6.5%	1,285	4.9%	1.39 (1.24-1.56)	1.15 (0.98-1.35)	1.11 (0.95-1.31)
Cumulative dose							
<250 mg	133	2.0%	498	1.9%	1.08 (0.89-1.31)	1.06 (0.76-1.48)	1.00 (0.71-1.40)
250-1,000 mg	145	2.1%	383	1.5%	1.52 (1.25-1.85)	1.50 (1.07-2.11)	1.42 (1.01-2.00)
≥ 1,000 mg	164	2.4%	404	1.5%	1.66 (1.37-2.00)	1.53 (1.06-2.20)	1.43 (0.99-2.07)
Average daily dose ^a							
≤ 400 µg	106	1.6%	359	1.4%	1.19 (0.95-1.48)	1.09 (0.86-1.38)	1.00 (0.79-1.28)
401-800 µg	113	1.7%	359	1.4%	1.28 (1.03-1.58)	1.08 (0.85-1.38)	1.05 (0.82-1.34)
801-1,600 µg	131	1.9%	333	1.3%	1.60 (1.31-1.97)	1.27 (0.98-1.63)	1.26 (0.97-1.63)
≥ 1,600 µg	58	0.9%	121	0.5%	1.94 (1.41-2.66)	1.46 (1.02-2.08)	1.47 (1.02-2.10)
Not classified ^d	34	0.5%	113	0.4%	1.21 (0.82-1.78)	1.14 (0.77-1.69)	1.03 (0.91-1.17)

a: Average daily dose: cumulative exposure divided by the treatment time (inhaled salbutamol equivalents).

b: Adjusted for indicators of the severity of the underlying respiratory disease (i.e. use of inhaled corticosteroids, inhaled anticholinergics, xanthines, acetylcystein, average daily dose of oral corticosteroids, use of nebulised medication, ≥ 1 exacerbations, and ≥ 1 asthma/COPD hospitalisations).

c: Adjusted for indicators of the severity of the underlying respiratory disease (listed under b) and general risk factors of fracture risk (i.e. use of benzodiazepines, hormone replacement therapy, antipsychotics, antidepressants, beta-blockers, anticonvulsants, antidiabetics, two or more NSAID prescriptions, disease modifying anti-rheumatic drugs, anaemia, mental disorders, cerebrovascular disease, heart failure, endocrine disorders and inflammatory bowel disease).

d: Not classified: average daily dose could not be determined for current beta-2 agonist users with only one prior prescription.

Table 3.4.3 Daily/cumulative dose of beta-2 agonists and risk of hip/femur fracture in patients not exposed to oral corticosteroids.

Beta-2 agonist use	Cases (n=6,274)	Controls (n=23,339)	Crude OR (95% CI)	Adjusted OR (95% CI) ^b
Never use	5,700	21,450	1.00	1.00
Past use	320	1,104	1.08 (0.95-1.23)	0.99 (0.87-1.14)
Current use	254	785	1.21 (1.04-1.39)	1.00 (0.83-1.21)
Cumulative dose				
<250 mg	90	349	0.98 (0.77-1.24)	0.86 (0.67-1.11)
250-1,000 mg	82	228	1.33 (1.03-1.72)	1.16 (0.87-1.54)
≥ 1,000 mg	82	207	1.45 (1.12-1.88)	1.15 (0.84-1.56)
Average daily dose ^a				
≤ 400 µg	65	245	0.99 (0.75-1.30)	0.84 (0.62-1.13)
401-800 µg	67	204	1.23 (0.93-1.63)	1.05 (0.77-1.42)
801-1,600 µg	71	185	1.43 (1.08-1.89)	1.19 (0.86-1.64)
≥ 1,600 µg	26	61	1.56 (0.98-2.48)	1.31 (0.80-2.15)
Not classified ^c	25	90	1.05 (0.67-1.64)	0.94 (0.59-1.48)

a: Average daily dose: cumulative exposure divided by the treatment time (inhaled salbutamol equivalents).

b: Adjusted for use of inhaled corticosteroids, inhaled anticholinergics, xanthines, acetylcystein, nebulised medication, ≥ 1 asthma/COPD hospitalisations, use of benzodiazepines, hormone replacement therapy, antipsychotics, antidepressants, beta-blockers, anticonvulsants, antidiabetics, two or more NSAID prescriptions, disease modifying anti-rheumatic drugs, anaemia, mental disorders, cerebrovascular disease, heart failure, endocrine disorders and inflammatory bowel disease.

c: Not classified: average daily dose could not be determined for current beta-2 agonist users with only one prior prescription.

adjustment for general risk factors of fracture risk did not modify the risk of hip/femur fracture (OR 1.12 [95% CI 0.95-1.31]).

The risk of hip/femur fracture increased with higher daily and cumulative dose of beta-2 agonists (Table 3.4.2). In patients using a daily dose of >1,600 µg salbutamol equivalents, the risk of hip/femur fracture was increased by 46% (OR 1.46 [95% CI 1.02-2.08]). There were no substantial differences between short-acting (OR 1.16 [95% CI 0.98-1.38] and long-acting beta-2 agonists (OR 0.97 [95% CI 0.74-1.27]). Figure 3.4.1 shows the association between time since last beta-2 agonist prescription and risk of hip/femur fracture. The risk of fracture was increased particularly in patients who were recently exposed to beta-2 agonists.

After exclusion of patients who were exposed to OCs, the risk of hip/femur was no longer statistically significantly increased in any of daily or cumulative dose categories of beta-2 agonists (Table 3.4.3). In patients using a daily dose of >1,600 µg salbutamol equivalents without prior exposure to OCs, the OR of hip/femur was 1.31 [95% CI 0.80-2.15]. To further examine the role of the severity of the underlying disease, we also evaluated the association between risk of hip/femur fracture and other respiratory medication. It was found that the risk of hip/femur fracture increased with higher daily doses of all different respiratory medication (Figure 3.4.2). The risk of hip/femur fracture was statistically similar between users of higher doses of beta-2 agonists, ICS or inhaled anticholinergics.

Discussion

In this study, we found increases in the risk of hip/femur fracture in patients using higher doses of beta-2 agonists. However, the excess risk of hip/femur fracture substantially reduced after exclusion of OC users and after adjustment for indicators of underlying disease severity. Also, the risk of hip/femur fracture was similar between users of beta-2 agonists, ICS and inhaled anticholinergics.

The autonomic nervous system is involved in regulation of bone remodeling. Leptin, a hormone that is produced in fat cells in order to signal food intake and body weight, regulates bone formation through the hypothalamus in mice.^{1,20} Downstream the sympathetic signaling, stimulation of beta-2 receptors present on osteoblasts progenitor cells, results in an increased bone resorption by expression of the osteoclast differentiation factor RANKL.² Systemic administration of beta-2 agonists like salbutamol and clenbuterol had a negative effect on bone mineral density and microarchitecture of trabecular bone in rats.³ Systemic administration of

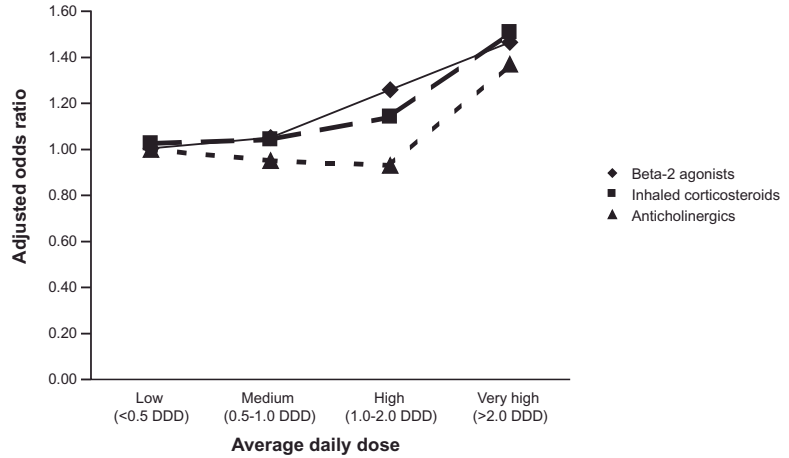


Figure 3.4.2 Risk of hip/femur fracture among current users of beta-2 agonists, inhaled corticosteroids or inhaled anticholinergics by average daily dose. Adjusted odds ratio: adjusted for the same indicators of severity of OAD and general risk factors as in Table 3.4.2, footnote c). DDD: Defined daily dose. 1 DDD is equivalent to 800 µg inhaled salbutamol, 800 µg inhaled beclomethasone dipropionate or 120 µg ipratropiumbromide.

clenbuterol inhibited femoral bone growth, and decreased bone mineral content and bone mineral density.²¹ Isoproterenol, another beta-2 agonist, has shown to suppress bone formation in mice. The same study revealed a specific role of the sympathetic nervous system in unloading-induced bone loss.²² Conversely, bone mineral density, bone mass and femoral torsional strength in rats were increased after systemic administration of the beta-blocker propranolol.^{1,4}

Observational studies in humans have shown conflicting results on the association between use of beta-blockers and reduced risk of fracture or increased in bone mineral density.^{5-7,23-25} Preliminary results from a randomised controlled clinical trial did not show a fracture risk reduction among users of the non-cardioselective beta-blocker carvedilol.²⁶ Another randomised controlled trial found that intake of the non-cardioselective betablocker propranolol did not change markers of bone formation.⁷ The reason for this lack of consistent effects of beta-blockers in humans is unknown. Although beta-blockers may have positive effects on the bone at very high doses in animals, this cannot generalise to humans with considerable lower doses. The concentration of beta-blockers in bone tissue is not known. For beta-2 agonists that are administered through inhalation, these levels are likely to be even lower. Average blood plasma concentration of salbutamol after in-

halation of 180 µg was found to be 1.5 ng/L compared to levels of carvedilol ranging from 21 to 161 µg/L after single 25-50 mg doses.^{8,27-29} As blood plasma concentrations of oral carvedilol are at least 10,000 times higher than inhaled salbutamol, it seems unlikely that salbutamol intake would affect bone mineral metabolism.

This study found that patients using different respiratory medications had increased risks of fracture, especially at higher daily dose. The explanation for this increase could be adverse effects of the three different classes of respiratory medication or effects of the underlying respiratory disease. Increases in the risk of fracture have been reported for ICS, but there is controversy about the explanation of this increased risk.^{15,30} There is no evidence for a causal relationship between intake of inhaled anticholinergics and risk of hip/femur fracture. Obstructive airway disease itself has been associated with decreased bone mineral density, independent of OC exposure.^{31,32} The underlying mechanisms for this may include lack of physical activity,^{33,34} low body mass index among patients with COPD,³⁵ smoking,³⁶ decreased testosterone levels,³⁷ hypercapnia³⁸ and chronic inflammation. Cytokines that are expressed in inflammatory diseases, such as asthma and/or COPD, include tumour necrosis factor (TNF)-alpha, transforming growth factor-beta, interleukin (IL)-1beta, IL-4 and IL-8. These cytokines have been shown to affect bone remodelling in vivo and in vitro.³⁹⁻⁴⁵ In this study, adjustment for several proxy indicators of disease severity substantially reduced the excess risk of fracture in patients using beta-2 agonists. Given the inverse association between lung function and bone mineral density,³¹ it appears likely that further adjustment with lung function would further decrease this small excess risk.

This study has several limitations. The PHARMO RLS database lacks detailed information on the severity of respiratory disease such as lung function measurements. But even with proxy indicators of disease severity, we found that the risk of hip/femur fracture reduced substantially after adjustment. Moreover, data on smoking³⁶, body mass index or fat free mass⁴⁶ and data on exercise were not available. Therefore, we cannot exclude the possibility that unmeasured confounding has biased our findings. But it is likely that adjustment for these factors would have further reduced the excess risk of hip/femur fracture in patients using beta-2 agonists. Also, we did not have information on the timing of drug intake by patients, only on the timing of drug dispensing. With more than 6,700 hip/femur fractures, our study had a reasonable sample size to study our hypothesis. We were able to match almost each case patient to up to 4 controls by age, gender and region in order to

minimise confounding by matching variables. Our findings of an increased risk of hip fracture with the use of OCs,⁴⁷ benzodiazepines,^{48,49} antidepressants,⁴⁸ and anticonvulsants⁵⁰ are similar to those of previous studies.

In conclusion, we found that patients who suffer from severe obstructive airway disease are at increased risk of hip/femur fracture. A dose-response association was apparent not only among users of beta-2 agonists, but also among users of other types of respiratory medications. This suggests that the severity of the underlying disease, rather than the use of beta-2 agonists, may play an important role in the aetiology of hip/femur fractures in patients using beta-2 agonists.

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Chapter 4.1

Evidence for No Association Between Use of Beta-2 Agonists and Risk of Acute Myocardial Infarction in Patients with Hypertension

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Summary

Objective. To examine the association between beta-2 agonist use and first non-fatal acute myocardial infarction (MI).

Methods. We conducted a case-control study (2,476 cases) nested in a cohort of antihypertensive drug users in the Dutch PHARMO RLS database. PHARMO RLS consists of drug dispensings linked to the national hospitalisations register. Each case of non-fatal acute MI was matched with up to 12 control patients by gender, age and region. We adjusted for drug and disease history, and the severity of the underlying respiratory disease.

Results. Risk of acute MI was increased in current beta-2 agonist users (crude OR 1.36 [95% CI 1.15-1.61]). However, this excess risk was reduced after adjustment for severity of asthma and COPD (adjusted OR 1.18 [95% CI 0.93-1.49]). The risk was highest in patients with ischaemic heart disease and low cumulative dose of beta-2 agonists (adjusted OR of 2.47 [95% CI 1.60-3.82]).

Conclusion. Most users of beta-2 agonists did not have an increased risk of acute MI. Only patients with ischaemic heart disease and who had recently started beta-2 agonists had an increased risk of acute MI. It is likely that this increased risk was related to latent cardiovascular disease rather than to the direct effects of beta-2 agonists.

Introduction

Beta-2 agonists are the most frequently used drugs in the treatment of obstructive airway disease (OAD), which is defined as asthma or chronic obstructive pulmonary disease (COPD). Although beta-2 agonists are usually inhaled with low systemic absorption, there have been reports of increased plasma levels.¹ Beta-2 receptors are present in the myocardium where they mediate contraction.² Through this mechanism, use of beta-2 agonists has been associated with tachycardia, an abnormal ECG and atrial fibrillation.³⁻⁵

Observational retrospective studies of the association between use of beta-2 agonists and risk of acute MI have demonstrated conflicting results, particularly among first-time users.⁶⁻⁸ Explanations for these discrepancies include a role of the underlying disease (COPD or hypertension) in the aetiology of MI and lack of statistical adjustment for use of beta-blockers or nebulised administration forms of respiratory medications. It has also been suggested that beta-2 agonists may be prescribed to patients with latent ischaemic heart disease, which has symptoms that appear similar to respiratory complaints in OAD.⁸ However, none of these hypotheses have yet been tested. Furthermore, previous studies have not quantified beta-2 agonist exposure in a very detailed fashion.⁶⁻⁸ Because cardiovascular diseases are highly prevalent in patients with COPD,^{9,10} our study aimed to examine the association between beta-2 agonists and first non-fatal acute MI in antihypertensive drug users, who represent a population at an increased risk of MI.

Methods

Base population

The setting of the study was the PHARMO record linkage system (RLS, www.pharmo.nl). PHARMO RLS includes the demographic details and complete medication history of more than two million community-dwelling residents in the Netherlands. These pharmacy data are then linked to hospital admission records as well as several other health registries, including pathology, clinical laboratory findings and general practitioner data. Since virtually all patients in the Netherlands are registered with a single community pharmacy, independently of prescriber, pharmacy records are virtually complete with regard to prescription drugs. Patients are included in the database regardless of their health insurance or socio-economic status, and represent about 13% of the general population. Several independent validation studies have shown that PHARMO RLS has a

high level of completeness and validity. For this study, only drug dispensing data and hospitalisation data from January 1991 through December 2003 were used.^{11,12} PHARMO RLS has previously been used to study drug-induced cardiovascular outcomes.^{13,14}

Cohort definition

Patients registered in the PHARMO RLS for at least one year and using antihypertensive drugs (thiazide diuretics, beta-blockers, calcium channel blockers, ace-inhibitors, angiotensin II receptor blockers or centrally acting agents) were included in the study population.

Study design

A nested case-control analysis was conducted within the cohort. The outcome of interest was the first non-fatal acute MI (International Classification of Diseases 9 (ICD-9) code 410) that occurred within 100 days after the last dispensing of antihypertensive drugs. A period of 100 days was selected as Dutch health insurance policies cover the dispensing of the majority of drugs for three months. We did not include patients who suffered from a fatal MI because they may have died before hospitalisation and then their MI data may not have been registered in PHARMO RLS. The date of first admission for non-fatal acute MI was defined as the index date. Only cases aged 18 years and older at the index date were included in the analysis. Each case was matched with up to 12 control patients by year of birth ($\pm$ two years), gender and geographical area. Control patients had similar eligibility criteria as cases. Controls were assigned the same index date as the case with whom they were matched.

Exposure

Current users of beta-2 agonists were defined as patients who received at least one dispensing within 100 days before the index date. Recent users received their last dispensing for beta-2 agonists in the 100 days up to one year before the index date, and past users were patients with their last dispensing at least one year before the index date. For current users, we calculated the cumulative dose and the average daily dose (calculated by division of the cumulative dose by the treatment time, expressed as inhaled salbutamol equivalents (eq.) using defined daily dosages.^{15,16} -salbutamol is a synonym of albuterol) Exposure to beta-2 agonists was also examined in patients with a history of ischaemic heart disease (i.e. patients who were exposed to at least one nitrate prescription¹⁷ or who had been hospitalised for ischaemic heart disease, or who had undergone a

percutaneous transluminal coronary angioplasty or coronary artery bypass graft).

Covariates

We adjusted our analysis for cardiovascular risk factors, defined as dispensings for antihypertensive drugs 100 days before the index date, non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin in the two months before, and loop diuretics, digoxin, antiarrhythmics, spironolactone, nitrates, statins, fibrates, anticoagulants, and antidiabetics in the six months before the index date. In addition, we adjusted for hospitalisations for hypertensive disease, diabetes mellitus, hyperlipidaemia, ischaemic heart disease, rheumatic heart disease, diseases of the pulmonary circulation, other forms of heart disease including heart failure and cardiac dysrhythmias, and cerebrovascular disease ever prior to the index date. Because of the reported inverse association between lung function and coronary heart disease,^{18,19} we also adjusted for indicators of the severity of the underlying respiratory disease, including hospitalisations for OAD in the one year before and exposure to inhaled corticosteroids (ICS), inhaled anticholinergics, xanthine derivatives, acetylcysteine, nebulised medications and oral corticosteroids (OCs, using the average daily dose) in the six months prior to the index date. Furthermore, we adjusted for antibiotics (tetracyclines, penicillins, beta-lactam antibacterials, sulphonamides and macrolides) within three days of an OC dispensing (a marker for an exacerbation of COPD²⁰).

Statistical analysis

We used conditional logistic regression (SAS version 9.1.3, PHREG procedure) to quantify the association between use of beta-2 agonists and risk of non-fatal acute MI. We conducted two differently adjusted analyses: firstly, we adjusted the results for the indicators of the severity of the underlying respiratory disease. Secondly, we also adjusted for cardiovascular risk factors using backward elimination. In order to visualise the relationship between risk of acute MI and recency of beta-2 agonist use (i.e. the time between the index date and the most recent dispensing) and cumulative beta-2 agonist use, we used smoothing spline regression plots (SAS version 9.1.3). In a sensitivity analysis, we restricted our analysis to patients who were likely to have a previous diagnosis of COPD. We used a COPD definition that has previously been used by Suissa et al.⁸ These patients were 55 years or older at the index date and had filled at least three dispensings for bronchodilators at two or more different dates in any one-year period before the index date.

Table 4.1.1 Baseline characteristics.

Characteristic	Cases		Controls	
	(n=2,476)	(%)	(n=24,252)	(%)
Mean age (years)	67.3		67.2	
Females	1,008	40.7%	1,0014	41.3%
Antihypertensive drug use in the 100 days before				
Thiazide diuretics	668	27.0%	8,275	34.1%
Beta-blockers	1,331	53.8%	11,401	47.0%
Calcium channel blockers	869	35.1%	6,232	25.7%
Ace inhibitors	685	27.7%	7,773	32.1%
Angiotensin II receptor blockers	233	9.4%	2,507	10.3%
Other antihypertensive drugs	20	0.8%	174	0.7%
Cardiovascular drug use in the 6 months before				
Lipid lowering drugs	526	21.2%	5,028	20.7%
Statins	512	20.7%	4,876	20.1%
Fibrates	31	1.3%	268	1.1%
Antidiabetic agents	406	16.4%	2,937	12.1%
Loop diuretics	299	12.1%	2,413	9.9%
Spironolactone	37	1.5%	361	1.5%
Potassium sparing diuretics	268	10.8%	3,049	12.6%
Anticoagulants	283	11.4%	2,838	11.7%
Digoxin	105	4.2%	1,243	5.1%
Antiarrhythmics other than digoxin	147	5.9%	1,625	6.7%
Nitrates	792	32.0%	3,276	13.5%
Respiratory drug use in the 6 months before				
Beta-2 agonists	216	8.7%	1,728	7.1%
Inhaled corticosteroids	196	7.9%	1,503	6.2%
Anticholinergics	138	5.6%	1,088	4.5%
Xanthine derivatives	32	1.3%	217	0.9%
Acetylcystein	84	3.4%	721	3.0%
Oral corticosteroids by daily dose				
<7.5 mg	44	1.8%	339	1.4%
7.5-15 mg	15	0.6%	173	0.7%
≥ 15 mg	10	0.4%	72	0.3%

Results

We identified a total of 2,476 subjects with an acute MI during follow-up. The mean age at the index date was 67 years and 59% of the cases were males. Almost all cases were matched with ten controls. Table 4.1.1 shows their baseline characteristics. As expected, cases were more likely to receive antidiabetics and drugs for the treatment of ischaemic heart disease. Indicators of the severity of OAD were associated with an increased risk of acute MI (crude odds ratio (OR) of 1.35 [95% confidence interval (CI) 1.10-1.64] with use of inhaled anticholinergics, OR of 1.37 [95% CI 1.15-1.63] with use of ICS, and OR of 1.69 [95% CI 0.91-3.10] with hospitalisation for OAD).

As shown in Table 4.1.2, the risk of acute MI was increased in current users of beta-2 agonists (crude OR 1.36 [95% CI 1.15-1.61]). After adjustment for severity of OAD, the excess risk was reduced and was statistically comparable to non-users (adjusted

OR 1.18 [95% CI 0.93-1.49]). There was no difference between current exposure to short-acting beta-2 agonists (adjusted OR 0.98 [95% CI 0.74-1.30]) or long-acting beta-2 agonists (adjusted OR 1.28 [95% CI 0.92-1.78]). The results also did not change when restricting the study population to patients with COPD.

Figure 4.1.1 shows that the risk of acute MI was increased particularly in patients who received their last beta-2 agonist prescription shortly before the index date. The adjusted OR for patients with a beta-2 agonist dispensing in the 30 days prior to the index date was 1.45 [95% CI 1.10-1.92]. High cumulative exposure to beta-2 agonists was not associated with an increased risk of acute MI (Figure 4.2.2). Recent starters (i.e. patients with low cumulative exposure (<0.25 g)) had the highest risks of acute MI (adjusted OR of 1.38 [95% CI 0.98-1.94]).

In order to further explore the higher risks in patients who received beta-2 agonists shortly before the index date and who had low cumulative exposure, the study population was stratified by history of ischaemic heart disease. It was found that current users of beta-2 agonists with a history of ischaemic heart disease had a two-fold increased risk of acute MI compared to non-users (Table 4.1.3). This risk was highest in patients with ischaemic heart disease and who had low cumulative dose of beta-2 agonists (i.e. recent starters, adjusted OR of 2.47 [95% CI 1.60-3.82]).

Figure 4.1.3 shows that current beta-2 agonist users with a history of ischaemic heart disease who recently started nitrates had a fourfold increased risk of acute MI (adjusted OR of 3.80 [95% CI 1.74-8.30]). The risk was reduced in those with long-term nitrate use (adjusted OR of OR 1.53 [95% CI 1.00-2.33] with ten or more prior nitrate dispensings).

Discussion

In our study population of patients receiving treatment for hypertension, those using beta-2 agonists were not associated with an increased risk of acute MI compared to non-users after adjustment for underlying respiratory disease severity. However, the risk was increased in recent starters of beta-2 agonist users who had a history of ischaemic heart disease.

Table 4.1.2 Use of beta-2 agonists and risk of acute MI.

Beta-2 agonist use	Cases (n=2,476)	(%)	Controls (n=24,252)	(%)	Crude OR (95% CI)	Adjusted OR (95% CI) ^b	Adjusted OR (95% CI) ^c
Never use	2,109	85.2%	21,231	87.5%	1.00	1.00	1.00
Recent use	68	2.7%	596	2.5%	1.16 (0.90-1.50)	1.09 (0.84-1.43)	1.07 (0.82-1.41)
Past use	133	5.4%	1,153	4.8%	1.17 (0.97-1.42)	1.15 (0.95-1.39)	1.13 (0.93-1.36)
Current use	166	6.7%	1,272	5.2%	1.36 (1.15-1.61)	1.18 (0.93-1.49)	1.16 (0.91-1.47)
Average daily dose ^a							
First time use	15	0.6%	98	0.4%	1.57 (0.91-2.72)	1.45 (0.83-2.53)	1.29 (0.74-2.27)
≤ 400 µg	50	2.0%	372	1.5%	1.37 (1.01-1.85)	1.19 (0.85-1.67)	1.13 (0.80-1.59)
401-800 µg	48	1.9%	370	1.5%	1.37 (1.01-1.86)	1.17 (0.82-1.66)	1.20 (0.84-1.72)
801-1,600 µg	45	1.8%	355	1.5%	1.33 (0.97-1.82)	1.08 (0.74-1.57)	1.12 (0.76-1.65)
≥ 1,600 µg	8	0.3%	77	0.3%	1.11 (0.53-2.30)	0.88 (0.41-1.91)	0.88 (0.41-1.90)

a: Average daily dose: cumulative exposure divided by the treatment time.

b: Adjusted for indicators of the severity of OAD included exacerbations, the use of inhaled corticosteroid, inhaled anticholinergics, xanthine derivatives, nebulised medication, daily dose of OCs (<7.5, 7.5-15, ≥ 15 mg), and acetylcysteine six months before index date. Hospitalisations for OAD one year before the index date were also considered an indicator of the severity of OAD.

c: Adjusted for indicators of the severity of OAD (*) and general risk factors of MI including the use of antidiabetics, statins, fibrates, nitrates, digoxin, thiazide diuretics, calcium channel blockers, beta-blockers, ACE inhibitors and angiotensin II receptor blockers six months prior to the index date, use of NSAIDs two months before index date, and a history of cardiovascular disease, pulmonary disease and rheumatoid arthritis ever before the index date.

Table 4.1.3 Use of beta-2 agonists and risk of acute MI according to history of ischaemic heart disease.

Beta-2 agonist use	No history of ischaemic heart disease			History of ischaemic heart disease		
	Cases (n=1,616)	Controls (n=20,295)	Adjusted ^a OR (95% CI) ^b	Cases (n=860)	Controls (n=3,957)	Adjusted ^a OR (95% CI) ^c
Current use^b	88	977	0.88 (0.67-1.17)	78	295	1.93 (1.41-2.65)
Average daily dose ^a						
First time use	9	74	1.13 (0.56-2.29)	6	24	1.69 (0.67-4.27)
≤ 400 µg	19	282	0.66 (0.41-1.08)	31	90	2.38 (1.50-3.76)
401-800 µg	27	294	0.92 (0.59-1.43)	21	76	2.11 (1.24-3.59)
801-1,600 µg	30	271	1.10 (0.71-1.71)	15	84	1.33 (0.73-2.43)
≥ 1,600 µg	3	56	0.49 (0.15-1.61)	5	21	1.84 (0.66-5.11)
Cumulative dose						
<250 mg	28	329	0.83 (0.55-1.25)	33	94	2.47 (1.60-3.82)
250-1,000 mg	23	330	0.72 (0.45-1.15)	28	106	1.91 (1.19-3.05)
≥ 1,000 mg	37	318	1.14 (0.76-1.72)	17	95	1.29 (0.72-2.29)

a: Fully adjusted for the same confounders as in Table 4.1.2 (model under footnote c), excluding the use of nitrates.

b: Referent: patients who were never exposed to beta-2 agonists before the index date

There are several possible explanations for our finding of an increased risk of acute MI in recent starters of beta-2 agonist users with a history of ischaemic heart disease. A likely explanation is that the dyspnoea-like symptoms were caused by latent cardiovascular disease rather than OAD. Acute ischemia or cardiomyopathy can increase the left ventricular end-diastolic volume. This mechanism has been associated with an increase in pulmonary vascular pressures, leading to dyspnoea either by producing hypoxemia or by stimulation of pulmonary vascular and/or interstitial receptors.²¹ Thus, these patients may have been prescribed beta-2 agonists due to similarity in clinical presentation. An alternative explanation for our findings is direct effects of beta-2 agonists in this

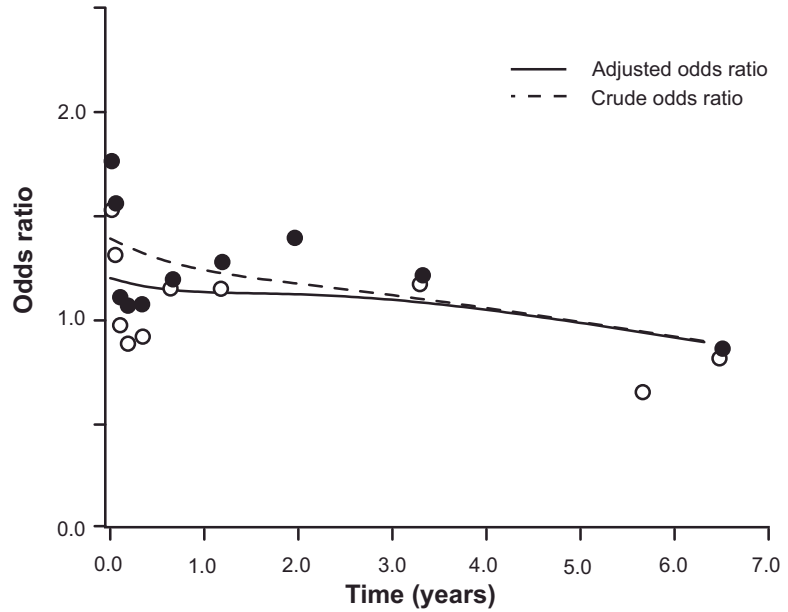


Figure 4.1.1 Risk of acute MI and time between index date and last dispensing for beta-2 agonists. Adjusted for confounders in Table 4.1.2, footnote c.

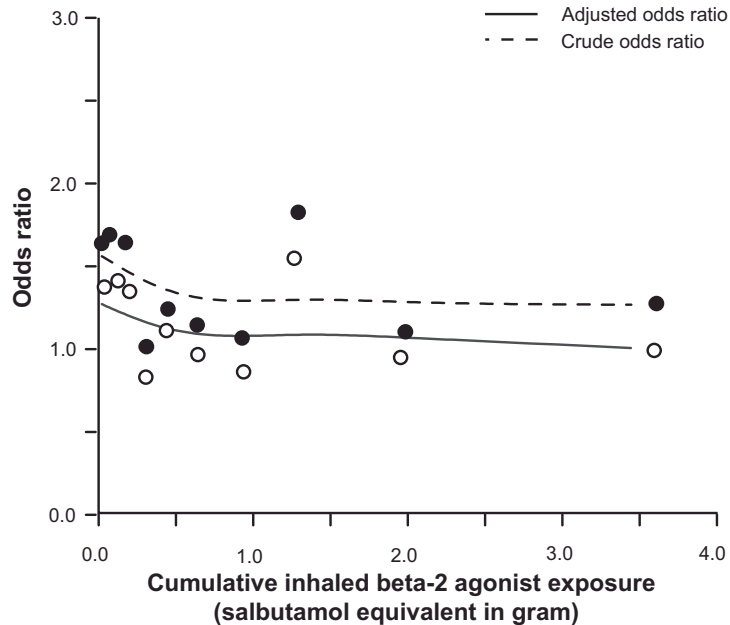


Figure 4.1.2 Risk of acute MI and cumulative dose of beta-2 agonists use among current users. Adjusted for confounders in Table 4.1.2, footnote c.

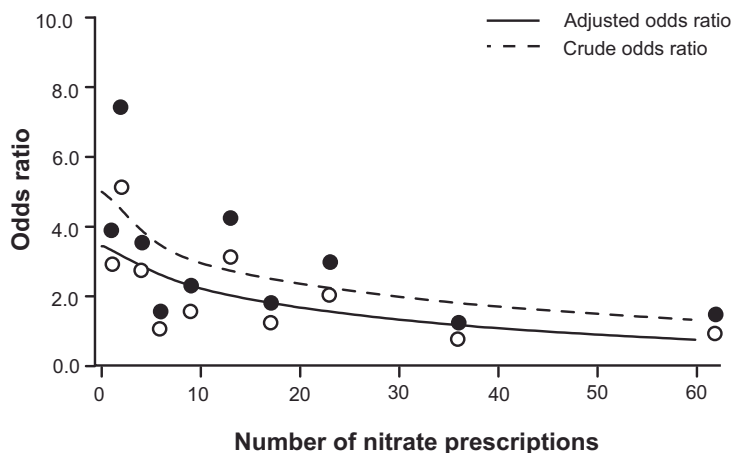


Figure 4.1.3 Risk of acute MI and number of previous nitrate dispensing in current users of both beta-2 agonists and nitrates. Adjusted for confounders in Table 4.1.2, footnote c, excluding nitrates.

subgroup of patients. It has been described that stimulation of cardiac beta-2 receptors may result in tachycardia, ECG changes, and atrial fibrillation.²⁻⁵ In dose-response studies, it has been demonstrated that higher beta-2 agonist dosages caused more severe cardiac side effects.^{22,23}

Through this mechanism, we would expect a positive association between daily or cumulative dose of beta-2 agonists and risk of acute MI. However, none of our dose analyses supported this hypothesis. Higher daily doses of beta-2 agonists were not associated with higher risks of acute MI and cumulative dose was inversely correlated with the risk of acute MI. The lack of direct effects of beta-2 agonists on the risk of acute MI are also supported by a meta-analysis of randomised controlled clinical trials that compared beta-2 agonist users to placebo. Although the risk of sinus tachycardia was increased threefold, no significantly increased risk of major cardiovascular outcomes (including acute MI) was found.^{24,25}

Although our main finding of a lack of association between use of beta-2 agonists and risk of acute MI is similar to the results from a Canadian case-control study,⁸ the differences in the statistical approaches of the two studies must be noted: the Canadian study evaluated three exposure categories by counting the number of dispensed canisters, and its analyses were stratified by history of cardiovascular disease. We chose to quantify the cumulative dispensed dose and the recency of use in a very detailed way using

smoothing spline visualisations. We stratified our analysis by ischaemic heart disease and number of nitrate prescriptions in order to identify high-risk patients. Our findings contradict that of a US case-control study that reported increased risk of acute MI in first-time users of beta-2 agonists. The American study only adjusted for cardiovascular risk factors and not for the severity of OAD and use of respiratory medications and beta-blockers. Also, it did not evaluate the possibility that beta-2 agonists may be prescribed to patients with symptoms of latent ischaemic heart disease rather than asthma/COPD.⁷ In our study, increased risk of acute MI was most apparent in patients who recently started beta-2 agonists and who had a history of ischaemic heart disease. Our finding of the lack of effect of long-term use of beta-2 agonists and risk of acute MI is consistent with all other published studies.^{7,8}

One of the limitations of our study was the inability to fully adjust for underlying disease because only hospital records were available. Severity of the underlying respiratory disease could only be determined with proxy indicators rather than the lung function parameters.^{18,19} However, the initially elevated crude MI risk already dropped towards the null value after adjustment for the proxy indicators of the severity of the underlying respiratory disease. Unfortunately, we did not have data on smoking which may be an important confounder. Another limitation is that our findings apply to users of antihypertensive drugs and cannot be extrapolated to all users of beta-2 agonists.

Nevertheless, our study is the largest study examining the association between use of beta-2 agonists and risk of acute MI in a high-risk population. Unlike other studies, we were able to analyse small exposure groups (using spline regression) rather than lumping different exposure in a few categories. Therefore, we were also able to stratify to patients with a history of ischaemic heart disease in a very detailed fashion. Another strength of our study is the virtually complete drug dispensing records that gave us the opportunity to calculate dispensed dosages, instead of counting canister numbers. This is important in the light of the wide variety in administration forms (e.g. metered dose inhalers, inhalation powder in capsules and disks), which had been available during the period of data collection. In the Netherlands, drug dispensings were reimbursed regardless of socio-economic status or employment. Moreover, drug-dispensing data were routinely collected since 94% of Dutch patients always receive their drug dispensings from the same pharmacy.²⁶

In conclusion, we found that the majority of beta-2 agonist users in our study population did not have an increased risk of non-

fatal acute MI. Only patients with ischaemic heart disease and who had recently started beta-2 agonists had an increased risk of acute MI. It is likely that this increased risk was related to latent cardiovascular disease rather than direct effects of beta-2 agonists. Cardiovascular risk assessment should be considered in users of beta-2 agonists and antihypertensive medication when suffering from ischaemic heart disease.

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Chapter 4.2

Use of Inhaled Corticosteroids and the Risk of Non-Fatal Acute Myocardial Infarction

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Submitted for publication.

Summary

Background. Use of inhaled corticosteroids (ICS) may reduce the risk of acute myocardial infarction (MI) through reductions in systemic inflammation and C-reactive protein.

Objectives. To examine the association between use of ICS and risk of non-fatal acute MI.

Methods. In the Dutch PHARMO RLS database, we conducted a case-control study (2,476 MI cases), nested in a cohort of anti-hypertensive drug users. ICS use 100 days before index date was compared to never use. We adjusted the analyses for the severity of the underlying respiratory disease and general drug & disease history.

Results. We found that ICS use was not associated with a decreased risk of MI in antihypertensive drug users after adjustment for the underlying respiratory disease severity, adjusted odds ratio (OR) 1.24 [95% CI 0.97-1.57]. A higher daily dose (adj. OR 1.82 [95% CI 0.80-4.13] and longer duration of use (adj. OR 1.28 [95% CI 0.90-1.81]) were not associated with a decreased risk of MI. An ICS dispensing in the 30 days before the index date was not protective but resulted in a 1.7-fold increased risk of MI.

Conclusion. Our results do not support the hypothesis that ICS protect against risk of MI by reduction of systemic inflammation.

Introduction

Inhaled corticosteroids (ICS) are used to suppress chronic inflammation in the airways of patients who suffer from asthma or Chronic Obstructive Pulmonary Disease (COPD).¹ C-reactive protein (CRP) is a marker of inflammation and has been associated with an increased risk of cardiovascular disease. Conversely, reductions of elevated levels of CRP (with statins) have been found to reduce the size of atherosclerotic plaques and risk of cardiovascular disease.^{2,3} Given the elevated CRP levels in patients with COPD⁴⁻⁶, it has been hypothesised that ICS may reduce the risk of acute myocardial infarction (MI) through reductions in systemic inflammation and CRP.

Unfortunately, randomised controlled trials addressing the relationship between use of ICS and cardiovascular disease have been too underpowered to focus specifically at the risk of MI.^{7,8} Two epidemiological studies have studied the connection between use of ICS and risk of acute MI in patients with COPD and asthma. But their findings were only partially in line with the underlying biological mechanism: the strongest reductions in the risk of MI would be expected with high dose or long-term use of ICS, but in contrast, the effects in the epidemiological studies occurred with low dose and short-term use of ICS.^{9,10} Given these conflicting results, we hypothesised that the small numbers of patients who were at high risk of acute MI in these epidemiological studies may have explained the lack of effect with long-term and high dose of ICS. Because hypertension is an important risk factor for cardiovascular disease, and elevated CRP levels have been positively associated with blood pressure and hypertension,¹¹ the objective of our study was to examine the association between use of ICS and the risk of non-fatal acute MI in users of antihypertensive drugs.

Methods

Base population

The setting of the study was the PHARMO record linkage system (RLS, www.pharmo.nl). PHARMO RLS includes the demographic details and complete medication history of more than two million community-dwelling residents in the Netherlands. These pharmacy data are then linked to hospital admission records as well as several other health registries, including pathology, clinical laboratory findings and general practitioner data. Since virtually all patients in the Netherlands are registered with a single community pharmacy, in-

dependent of prescriber, pharmacy records are virtually complete with regard to prescription drugs. Patients are included regardless of their health insurance or socio-economic status, and represent about 13% of the general population. Several independent validation studies have shown that PHARMO RLS has a high level of completeness and validity. For this study, only drug dispensing data and hospitalisation data from January 1991 through December 2003 were used.^{12,13}

Cohort definition

In PHARMO RLS, subjects who used antihypertensive drugs (thiazide diuretics, beta-blockers, calcium channel blockers, ace-inhibitors, angiotensin II receptor blockers or centrally acting agents) were included in the study population. Patients had to be registered in PHARMO RLS for at least one year.

Study design

A nested case-control analysis was conducted within the cohort. The outcome of interest was the first nonfatal acute MI (International Classification of Diseases 9 (ICD-9) code 410) that occurred within 100 days after the last dispensing of antihypertensive drugs. A period of 100 days was selected as Dutch health insurance policies cover the dispensing of the majority of drugs for periods of three months. We did not include patients who suffered from fatal MIs because they may have died before hospitalisation and these MIs are not recorded in PHARMO RLS. The date of the first admission for a non-fatal acute MI defined the index date. Only cases aged 18 years and older at the index date were included in the analyses. Each case was matched with up to 12 control patients by year of birth ($\pm$ two years), gender and geographical area. Control patients had the same eligibility criteria as cases. Controls were assigned the same index date as the case to whom they had been matched.

Exposure

Current users of ICS were defined as patients who received at least one dispensing within 100 days before the index date. Recent users received their last dispensing for ICS in the 100 days up to one year before the index date and past users were patients with their last dispensing at least one year before the index date. For current users, we calculated the average daily dose (DD, calculated by division of the cumulative dose by the treatment time, expressed as inhaled beclomethasone equivalents (eq.) using defined daily dosages.^{14,15}) The expected duration of ICS use was based on the prescribed drug

supply and prescribed daily dose (as determined from the dosage instructions). In case of overlap between two dispensing (i.e., a repeat dispensing filled within the duration of use for a previous dispensings), or a repeat dispensings filled within 90 days after discontinuation of the previous period, this period was then extended. In case of missing data on daily dose, the median expected duration of use was used.

Covariates

We adjusted our analysis for cardiovascular risk factors, defined as dispensings for antihypertensive drugs 100 days before the index date, non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin in the two months before, and loop diuretics, digoxin, antiarrhythmics, spironolactone, nitrates, statins, fibrates, anticoagulants, and antidiabetics in the six months before the index date. In addition, we adjusted for hospitalisations for hypertensive disease, diabetes mellitus, hyperlipidaemia, ischaemic heart disease, rheumatic heart disease, disease of the pulmonary circulation, other forms of heart disease including heart failure and cardiac dysrhythmias, and cerebrovascular disease ever prior to the index date. Because of the reported inverse association between lung function and coronary heart disease,^{16,17} we also adjusted for indicators of the severity of the underlying respiratory disease, including hospitalisations for asthma/COPD in the one year before and exposure to adrenergic beta-2 agonists, inhaled anticholinergics, xanthine derivatives, acetylcystein, nebulised medications and oral corticosteroids (OCs, using the average daily dose) in the six months prior to the index date. Furthermore we adjusted for antibiotics (tetracyclines, penicillins, beta-lactam antibacterials, sulphonamides and macrolides) within 3 days of an OC dispensing (a marker for an exacerbation of COPD).¹⁸ In a sensitivity analysis, we restricted our analysis to patients who were likely to have a previous diagnosis of COPD. We used a COPD definition that has previously been used by Huiart et al.¹⁰ These patients were 55 years or older at the index date and had filled at least three dispensings for bronchodilators at more than two different dates in any one-year period before the index date.

Statistical analysis

We used conditional logistic regression (SAS version 9.1.3, PHREG procedure) to quantify the association between use of ICS and risk of MI. We conducted two different adjusted analyses. Firstly, we adjusted the results for the indicators of the severity of the underlying respiratory disease.

Table 4.2.1 Baseline characteristics.

Characteristic	Cases		Controls	
	(n=2,476)	(%)	(n=24,252)	(%)
Mean age (years)	67.3		67.2	
Females	1,008	40.7%	1,0014	41.3%
Antihypertensive drug use in the 100 days before				
Thiazide diuretics	668	27.0%	8,275	34.1%
Beta-blockers	1,331	53.8%	11,401	47.0%
Calcium channel blockers	869	35.1%	6,232	25.7%
Ace inhibitors	685	27.7%	7,773	32.1%
Angiotensin II receptor blockers	233	9.4%	2,507	10.3%
Other antihypertensive drugs	20	0.8%	174	0.7%
Cardiovascular drug use in the six months before				
Lipid lowering drugs	526	21.2%	5,028	20.7%
Antidiabetic agents	406	16.4%	2,937	12.1%
Potassium sparing diuretics	268	10.8%	3,049	12.6%
Anticoagulants	283	11.4%	2,838	11.7%
Digoxin	105	4.2%	1,243	5.1%
Antiarrhythmics other than digoxin	147	5.9%	1,625	6.7%
Nitrates	792	32.0%	3,276	13.5%
Respiratory drug use in the six months before				
Beta-2 agonists	216	8.7%	1,728	7.1%
Anticholinergics	138	5.6%	1,088	4.5%
Xanthine derivatives	32	1.3%	217	0.9%
OCs by daily dose				
<7.5 mg	44	1.8%	339	1.4%
7.5-15 mg	15	0.6%	173	0.7%
≥15 mg	10	0.4%	72	0.3%

Secondly, we additionally adjusted for cardiovascular risk factors using backward elimination. In order to visualise the relationship between risk of acute MI and recency and cumulative dose of ICS use, we used smoothing spline regression plots (SAS version 9.1.3).

Results

A MI occurred in 2,476 subjects during follow-up. Table 4.2.1 shows the baseline characteristics of cases and controls. The patients were mostly elderly with a mean age of 67 years and 59% were males. Cases were more likely to receive drugs that may be used for treatment of diabetes and ischaemic heart disease (nitrates, beta-blockers and calcium channel blockers). Indicators of the severity of respiratory disease that were associated with an increased risk of MI included the use of adrenergic beta-2 agonists (crude odds ratio (OR) 1.36 [95% confidence interval (CI) 1.15-1.61]), and the use of inhaled anticholinergics (crude OR 1.35 [95% CI 1.10-1.64]).

Table 4.2.2 Use of ICS and risk of non-fatal acute MI.

Inhaled corticosteroid use	Cases (n=2,476)	(%)	Controls (n=24,252)	(%)	Crude OR (95% CI)	Adjusted OR (95% CI) ^b	Adjusted OR (95% CI) ^c
Never use	2,154	87.0%	21,484	88.6%	1.00	1.00	1.00
Past use	93	3.8%	967	4.0%	0.99 (0.79-1.23)	0.97 (0.78-1.22)	0.95 (0.76-1.18)
Recent use	68	2.7%	596	2.5%	1.13 (0.87-1.46)	1.06 (0.81-1.40)	1.09 (0.83-1.43)
Current use	161	6.5%	1,205	5.0%	1.37 (1.15-1.63)	1.20 (0.95-1.53)	1.24 (0.97-1.57)
Average daily dose ^a							
First time use	15	0.6%	71	0.3%	2.14 (1.22-3.75)	1.93 (1.08-3.43)	1.75 (0.97-4.13)
≤ 400 µg	46	1.9%	323	1.3%	1.45 (1.06-1.99)	1.33 (0.94-1.88)	1.35 (0.95-1.91)
401-800 µg	47	1.9%	411	1.7%	1.16 (0.85-1.57)	1.02 (0.72-1.44)	1.06 (0.75-1.52)
801-1,600 µg	45	1.9%	362	1.5%	1.29 (0.94-1.77)	1.04 (0.71-1.53)	1.10 (0.75-1.62)
≥ 1,600 µg	8	0.3%	38	0.2%	2.17 (1.01-4.65)	1.74 (0.77-3.91)	1.82 (0.80-4.13)

a: Average daily dose: cumulative exposure divided by the treatment time (inhaled beclomethasone equivalents)

b: Adjusted for indicators of severity of obstructive airway disease included: use of adrenergic beta-2 agonists, inhaled anticholinergics, xanthine derivatives, nebulised medication, daily dose of oral corticosteroids (<7.5, 7.5-15, ≥ 15 mg), and acetylcysteine six months before index date; exacerbations six months before the index date and hospitalisations for asthma/COPD one year before the index date.

c: Adjusted for indicators of severity of obstructive airway disease (b) and general risk factors: use of antidiabetics, statins, fibrates, nitrates, digoxin, thiazide diuretics, calcium channel blockers, beta-blockers and ace inhibitors six months prior, NSAIDs two months before index date, and a history of cardiovascular disease, pulmonary disease and rheumatoid arthritis.

Table 4.2.2 shows that the risk of MI was increased among current users of ICS (crude OR 1.37 [95% CI 1.15-1.63]). After adjustment for indicators of the severity of the underlying respiratory disease, the magnitude of this excess risk of MI decreased and was no longer statistically significantly increased (adjusted OR 1.20 [95% CI 0.95-1.53]). The excess risk of MI was not different between men and women and young (< 70 years) and elderly (≥70 years) patients (data not shown). As shown in Figure 4.2.1, the risk of MI was increased 1.5-2.0-fold in patients who were dispensed an ICS shortly before the index date. A filled dispensing within 30 days before the index date resulted in an adjusted OR of 1.73 [95% CI 1.36-2.21]. Figure 4.2.2 shows that the average daily dose of ICS exposure was not associated with the excess risk of MI. The excess risk of MI was comparable between users of low and high dose ICS.

Figure 4.2.3 shows the association between duration of ICS treatment and excess risk of MI. No effect was observed of the duration of ICS use. The adjusted OR for short-term use (<1.0 year) was 1.17 [95% CI 0.87-1.56]), for medium term use (1.0-2.5 years) 1.41 [95% CI 0.88-2.27] and for long-term use (>2.5 years) 1.28 [95% CI 0.90-1.81]. In a sensitivity analysis, we were not able to mimic the results of a previous dose-response analysis in Canadian patients with COPD.¹⁰ In order to do this, we modified our current use time-window to 45 days, and focused on the use of ICS in patients with COPD who were also users of antihypertensive drugs. The excess risk of MI was not associated with DD of ICS.

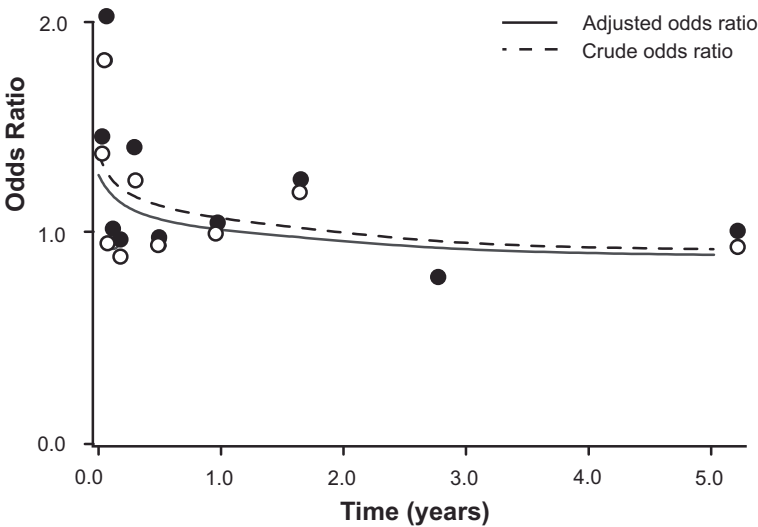


Figure 4.2.1 Time since last ICS prescription and risk of non-fatal acute MI. Adjusted odds ratios (open circles) were adjusted for the indicators of severity of obstructive airway disease and general risk factors as shown in Table 4.2.2, footnote c.

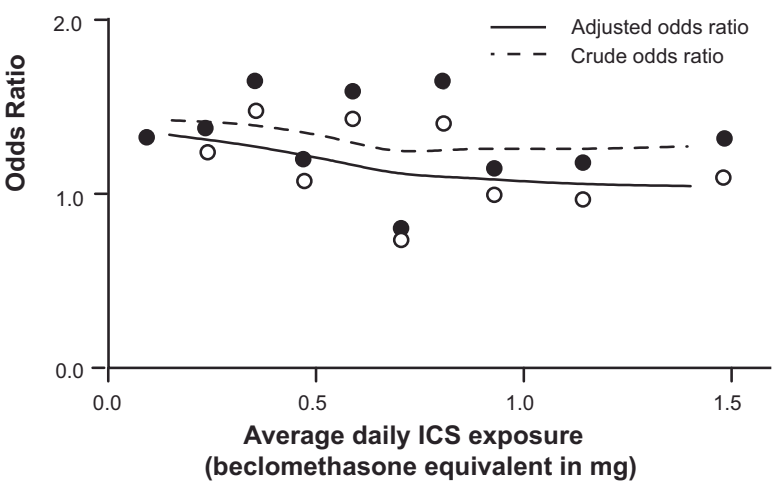


Figure 4.2.2 Average daily dose of ICS and the risk of non-fatal acute MI in current users of ICS. Adjusted odds ratios (open circles) were adjusted for the indicators of severity of obstructive airway disease and general risk factors as shown in Table 4.2.2, footnote c.

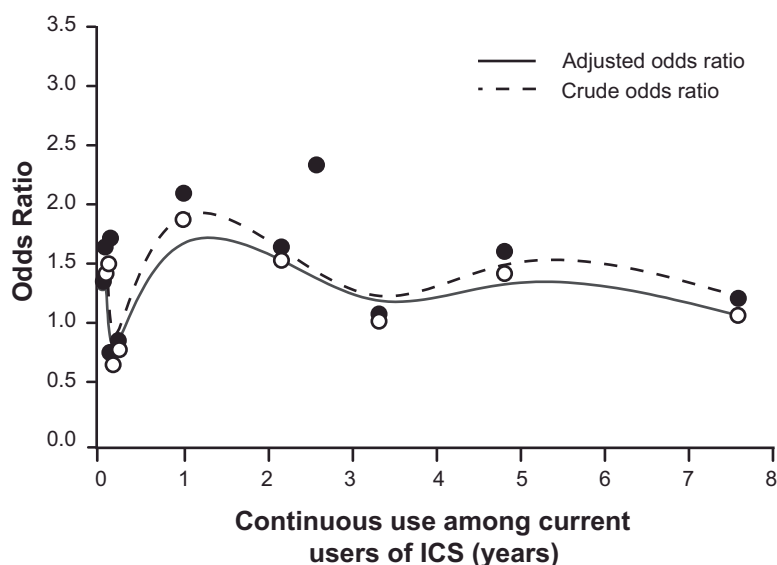


Figure 4.2.3 Duration of continuous use of ICS risk of non-fatal acute MI in current users of ICS. Adjusted odds ratios (open circles) were adjusted for the indicators of severity of obstructive airway disease and general risk factors as shown in Table 4.2.2, footnote c.

The adjusted OR was 1.19 [95% CI 0.34-4.24] with a DD of ≤ 200 μg , 0.99 [95% CI 0.44-2.24] with a DD of 200-500 μg and 1.12 [95% CI 0.72-1.74] with a DD of >500 μg . Another sensitivity analysis showed that our pivotal results of no association between ICS use and risk of MI remained unchanged when we stratified to current ICS users, who had never been exposed to beta-2 agonists or inhaled anticholinergics (adjusted OR 1.41 [95% CI 0.98-2.03]). We evaluated protopathic bias (i.e. the prescribing of respiratory medications as a result of symptoms (dyspnoea) of silent ischaemic heart disease) by stratification of ICS use by a history of ischaemic heart disease or nitrate dispensings.^{19,20} Risk of MI was doubled in patient with ischaemic heart disease, adjusted OR 2.06 [95% CI 1.49-2.85], in contrast to ICS users who did not have a history of ischaemic heart disease, adjusted OR 0.95 [95% CI 0.72-1.26].

Discussion

We found that ICS use was not associated with a decreased risk of MI in antihypertensive drug users after adjustment for the underlying respiratory disease severity. In addition, a higher daily dose and a longer duration of ICS use were not associated with a decreased risk of MI. Furthermore, an ICS dispensing in the 30 days before

the index date was not protective but was associated with a 1.7-fold increased risk of MI.

Several mechanisms for a possible protective effect of ICS on the risk of MI have been suggested in literature. These include improved asthma control, a reduction of exacerbations or episodes of hypoxemia, and related tachycardia.⁹ Also, a substantial reduction of elevated CRP levels in patients with COPD may reduce the size of atherosclerotic plaque and then reduce the risk of MI.⁶ In patients with COPD, biomarkers of systemic inflammation, including CRP, have been demonstrated to be inversely correlated with lung function.²¹ Decreased CRP levels resulted in substantial lower volumes of atheromae in patients with coronary artery disease.² In addition, there is evidence that statin-induced reduction of CRP levels results in lower risks of recurrent MI and death, especially after longer durations of use.³ In patients with COPD, two weeks exposure to high dose ICS reduced elevated plasma levels of CRP by 50%, whereas withdrawal increased CRP levels by 71%.⁵

Our key finding is that there is no association between ICS use and risk of MI. This is supported by findings of a two large randomised controlled trials that assessed the risk of cardiovascular outcomes in users of budesonide or fluticasone respectively.^{7,8} In a reanalysis of the ISOLDE trial, the adjusted relative rate of death with a cardiovascular cause was 0.98 95% CI [0.59-1.62].⁷ Preliminary results from the TORCH trial (6,184 COPD patients) showed no difference in cardiovascular adverse events between users of fluticasone or placebo.⁸ Two epidemiological studies have demonstrated results that are partially in line with our findings.^{9,10} In a cohort of Canadian patients with asthma, the use of ICS was associated with a two-fold reduction of MI risk.⁹ However, in the light of findings that plasma CRP is not decreased among ICS users with asthma, the aetiologic role of reduction of systemic inflammation has become less likely.²² Similar to our results, there was no overall association between use of ICS and risk on MI in a cohort of Canadian patients with COPD. Also, a longer duration of use or a higher daily dose of ICS did not result in a reduced risk of MI. However, the authors demonstrated a 30% reduced risk of MI in low dose ICS users.¹⁰ This was an unexpected result given the underlying biological hypothesis, because a randomised clinical trial in COPD patients reported a 50% reduction in CRP levels after exposure to ICS in dosages that were 6-26 times higher than reported by the authors of the Canadian observational study.^{5,10,15}

Our finding of a 1.7-fold increased risk of MI in ICS users 30 days before the index date may be explained by protopathic bias, namely complaints like shortness of breath that are caused by an

unrecognised, latent ischaemic heart disease, while these symptoms are treated with respiratory medications. This assumption is supported by our finding of a doubled risk of MI among users of ICS with a history of ischaemic heart disease. In addition, a systematic review of 1,837 MI diagnoses in a similar hospital database revealed that not a MI diagnosis, but signs and symptoms like chest pain (65%) and shortness of breath (22%) were the most frequent reasons for admission to the hospital.²³

This study has several limitations. We did not have data on body mass index or smoking, which may be important potential confounders. Although smokers are more likely to sustain a MI and to be exposed to ICS, no differences in CRP levels could be detected between smokers and non-smokers without COPD.⁴ Furthermore, we did not have data on CRP levels, or changes in atherosclerotic plaque size over time. Also, our study was conducted in a cohort of hypertensive subjects and our findings may not be generalised to users of ICS without hypertension. Our choice to limit our study population to hypertensive subjects was based on evidence that CRP levels are increased in patients with hypertension.⁹ Therefore, a cardioprotective effect of ICS could be more likely in this population.

A major strength of our study is that the findings are in line with the pivotal results from two large randomised clinical trials.^{7,8} Moreover, we examined the largest study population that was at high risk of myocardial infarction. For each patient, we had a virtually complete register of drug dispensings. Also, we had the opportunity to adjust our results for markers of the underlying respiratory disease severity, which turned out to be important confounder variables.^{9,14,24}

In conclusion, we did not find an inverse association between the use of ICS and risk of non-fatal acute MI in users of antihypertensive drugs after adjustment for respiratory disease severity. None of our exposure analyses (recency of use, duration of use, average daily dose) obviously supported the hypothesis that ICS may protect against risk of MI by reducing systemic inflammation. The severity of the underlying respiratory disease was an important confounder in the association between ICS use and risk of MI. Our results do not support the hypothesis that ICS protect against risk of MI by reduction of systemic inflammation.

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Chapter 5

Discussion

5.1 The challenge of establishing causality studying drug safety

Lack of evidence for corticosteroid-induced osteoporosis

In 1984, a systematic review of medical literature was conducted in order to evaluate the causal relationship between use of corticosteroids and osteoporosis. This review followed regulatory warnings of an increased risk of osteoporosis and vertebral fracture among users of systemic corticosteroids. The epidemiologists, Gordon Guyatt and David Sackett, who are cofounders of “evidence-based medicine”, hierarchically determined the degree of available evidence and stated:

“The conclusion to be drawn from this review is that the evidence that exogenous adrenocorticosteroids cause clinically important osteoporosis is weak. (...) When facing a difficult decision about commencing or continuing treatment, physicians should be mindful that the relation between steroids and osteoporosis is unproven. Further, they should consider that given the conflicting results of available studies (in the presence of a bias towards the finding of an elevated risk), any relation that does exist is unlikely -at least at exposures of less than 30 mg prednisone per day for prolonged periods- to be a strong one.”¹

The increased risk of fracture related to use of oral corticosteroids (OCs) has been well established since 2000.²⁻⁶ Nevertheless, even with the limited knowledge of OC-induced osteoporosis that existed at the time of Guyatt’s review, his interpretation of the available evidence remains noteworthy. Although carefully worded, using “unlikely” instead of “untrue”, the clinical message was that long-term exposure to less than 30 mg prednisone/day does not cause osteoporosis.

Issues with data

What were the main pitfalls of Guyatt’s review that may have lead to his inaccurate interpretation? From our present perspective, there may be least two explanations: issues related to the available data, or problems with Guyatt’s interpretation of causal inference. At the time of data extraction (1983), bone densitometry techniques, such as dual photon absorptiometry and neutron activation analysis, had just been introduced and dramatically improved the osteoporosis diagnosis in terms of precision and usefulness.⁷ But the systematic review included many studies that had been conducted in the seventies or earlier and thus its conflicting result is not surprising. Additionally, in-vivo and in-vitro studies that exam-

ined the underlying biological mechanism of corticosteroid-induced osteoporosis reported contrasting results. These limitations were acknowledged in the systematic review and used to rule out causation.¹

Issues with interpretation

The investigators conducted a so-called “diagnostic test for causation” that was based partially on nine viewpoints of causality proposed by Austin Bradford Hill.⁸ It included assessment of the strength, the consistency, the temporal relation, the dose-response gradient and biological plausibility of the association. After applying this test to each included study, the authors made a decision as to whether “weak” study designs had to be taken into account in the final conclusion.¹

The main problem with this approach lies in the assumption that the likelihood of causality could be solved by a set of rules. Although overlooked by many epidemiologists who applied his nine viewpoints, Hill had explicitly stated that cause-effect decisions could not be based on hard-and-fast rules of evidence.⁸ There are counterexamples of associations that show that Hill’s viewpoints cannot be used to rule out causation. For example, in the review by Guyatt et al, a lack of consistency (i.e. a repeated observation of association in different populations under different circumstances) does not rule out a causal association because some effects are produced by their causes only under unusual circumstances. Although biologic plausibility is important for the evaluation of a hypothesis, biological mechanisms are often only partially understood. As a result, it would be very difficult or even impossible to determine when biological plausibility can be used as criterion to rule out causality.⁹ Certainly, Guyatt’s classification of observational research as “weak”, in combination with the approach to Hill’s viewpoints, has contributed to the conclusion that a causal relationship between long-term use of OCs in daily dosages <30 mg and osteoporosis was unlikely. Alternatively, “unclear” instead of “unlikely” would have been a more balanced interpretation.

OC-induced osteoporosis: confounding by disease severity?

Another strategy for the evaluation of causal inference in epidemiology is a deductive approach in which non-causal explanations for estimated associations are excluded.¹⁰ Information from all types of study designs, from case reports to randomised clinical trials (RCTs), can be integrated with elements of Hill’s viewpoints in order to test a hypothesis that is a priori specifically enough phrased

in terms of magnitude, strength and gradients. Similarly, specific scenarios of (indirect) competing (or alternative) hypotheses and bias can be tested in order to increase the plausibility of the main hypothesis.^{9,10}

The specific phrasing of hypothesised bias highlights another parallel between the review by Guyatt et al and the issue of confounding by disease severity in the study of inhaled corticosteroid (ICS) use and osteoporosis/hip fracture. Guyatt et al suggested that confounding by the severity of asthma or rheumatoid arthritis might have resulted in the increased risk of osteoporosis and risk of fracture among users of OC users. He proposed that severely ill patients were less likely to be exposed to sunlight and exercise and were therefore at an increased risk of osteoporosis.¹ Although the magnitude and plausibility of this hypothesised confounding by indication were not estimated or tested, the hypothesised bias was clearly stated enough to be evaluated. Almost two decades later, the evaluation of confounding by disease severity was still largely ignored when linking ICS use with low bone mineral density (BMD) and risk of hip fracture.^{11,12}

5.2 Strategies for dealing with bias and confounding by disease severity

The main aim of this thesis was to examine the association between use of ICS and the risk of fracture, in the light of confounding by the respiratory disease severity. Before a number of general approaches of dealing with bias and confounding by respiratory disease severity are discussed, its potential underlying mechanisms are explained.

Confounding by disease severity is usually a multi-factorial phenomenon involving many factors that may act in different directions.¹³ A previous hypothesis that the severity of obstructive airway disease (OAD) would act as a positive confounder (i.e. increasing the risk of fracture among users of ICS) was supported by the finding that BMD was decreased in patients with respiratory disease, regardless of OC exposure.^{14,15} In addition, there are several other sources of confounding of the association between OAD and increased risk of fracture or osteoporosis. These include a lack of physical activity,^{16,17} low body mass index (BMI),¹⁸ smoking,¹⁹ decreased exposure to sunlight,¹⁴ decreased testosterone levels,²⁰ hypercapnia²¹ loss of fat-free mass^{22,23} and chronic inflammation. Cytokines that are expressed in inflammatory diseases, such as asthma and/or Chronic Obstructive Pulmonary Disease (COPD), include tumour necrosis factor (TNF)-alpha, transforming growth factor-

beta, interleukin(IL)-1beta, IL-4 and IL-8. These cytokines have been shown to affect bone remodelling in vivo and in vitro.²⁴⁻³⁰

Statistical control and confounding

In **Chapters 3.2** and **3.3**, we statistically controlled for confounding by respiratory disease severity in the dose-response association between use of ICS and risk of osteoporotic fracture. A set of indicators of disease severity (confounder variables) was identified in order to adjust the exposure outcome relationship using conditional logistic regression. Examples of confounder variables included the use of nebulised formulations, asthma/COPD hospitalisations or exacerbations in the year before the index date and the use of other respiratory medications. Statistical adjustment is a frequently applied technique for dealing with confounding in observational studies.³¹ This method is often applied to adjust for respiratory disease severity in pharmacoepidemiology.^{32,33}

We determined the association between use of beta-2 agonists and risk of hip/femur fracture. The results showed that the excess fracture risk substantially reduced after adjustment for disease severity indicators (**Chapter 3.4**). A similar shift towards the null value, but of a smaller magnitude, was observed when adjusting the association between use of beta-2 agonists/ICS and risk of acute myocardial infarction (MI) for respiratory disease severity indicators (**Chapters 4.1** and **4.2**). Alternatively, overadjustment could have occurred when (indicators of) disease severity were in the causal pathway of use of ICS and risk of fracture or MI. Overadjustment is the result of adjustment for a broad range of factors that are not truly confounders,³⁴ and it may be an alternative explanation for a shift of the point estimate towards the null value. However, given the marginally beneficial effects of ICS use on severity of COPD in experimental study designs (i.e. pulmonary function, rate of hospitalisations and rate of physician visits), overadjustment is unlikely to have occurred in **Chapters 3.2, 3.3** and **4.2**.^{35,36}

Stratification is an alternative method for dealing with confounding. An example of stratification by disease severity is demonstrated in Table 3.2.3. This table shows that patients with more severe OAD had higher risks of fracture, and these risks were comparable between users and nonusers of ICS. Indicators of disease severity may be used as multiple matching variables, a method that has been frequently applied in nested case-control studies by Suissa and co-workers.³⁷ This technique was not used in this thesis. **Chapter 2.1** presents a comparison of the procedures used for matching of variables in two studies: a relatively large study population versus

a small, selected study population with more variables. Our study demonstrated for the first time that an increasing number of matching variables in small, selected study populations (such as a nested-case control study) could result in an imbalanced selection of controls. Another disadvantage of stratification and matching techniques is the limited number of available strata. A major advantage of both methods is the possibility of clear communication of results.³¹

The general disadvantage of the use of indicators of disease severity is their limited usefulness for the precise measurement of the “true” severity of the respiratory disease.³⁸ This may have resulted in residual confounding by disease severity in **Chapters 3.2** through **4.2**.

Case-crossover and related study designs

Under certain conditions, a case-crossover approach could theoretically deal with (residual) confounding by disease severity. This approach is a variation of the matched case-control study. It has been developed in order to eliminate immeasurable differences between cases and controls. Within case-patients only, exposure status in “event periods” is compared with exposure status in “control periods”.³⁹ A variation is the case-time-control design, which additionally takes changes of exposure over time into account. For both study designs, one of the conditions is an exposure that has a short induction and transient effects. For example, Suissa and co-workers evaluated the association between the use of beta-2 agonists and the risk of fatal or near-fatal asthma in a Canadian study population. A case-control study design yielded an adjusted odds ratio (OR) of 3.1 [95% confidence interval (CI) 1.8-5.4], whereas a case-time-control approach to reduce confounding by respiratory disease severity estimated an OR of 1.2 [95% CI 0.5-3.0].⁴⁰

The condition that the exposure should have a short induction and transient effect is the reason that a case-crossover design was not useful in the evaluation of use of respiratory medications and risk of osteoporotic fracture, or ICS and risk of MI (**Chapters 3.2-3.4** and **4.2**). Theoretically, this condition could have been met in **Chapter 4.1**, where we studied the association between beta-2 agonist use and the risk of MI. However, it was not considered as a useful option: unlike (near) fatal asthma,⁴⁰ the study of a cardiac outcome among users of beta-2 agonists may be prone to protopathic bias (i.e. transient dyspnoea-like symptoms of latent ischaemic heart disease, may have resulted in prescribing of beta-2 agonists, showing a false-positive association).^{41,42} This was supported by the strong association of MI with recent ischaemic heart disease

(four-fold increase) among current users of beta-2 agonists (Figure 4.2.3).

In contrast to protopathic bias, reverse protopathic bias can explain inverse associations between exposure and outcome in observational studies. It occurs when the likelihood of exposure decreases by early (subclinical) stages of disease. This was, for example, demonstrated in a study that evaluated protective effects of alcohol on the formation of gallstones: presence of gallstones leads to a lower alcohol consumption, which may result in an imbalance in study base patients who are hospitalised for gallstone disease and are less likely to use higher amounts of alcohol compared to control patients selected from a general population.⁴³ Reverse protopathic bias has also been suggested as an explanation for previous findings from observational studies that found a beneficial association between dementia and the use of nonsteroidal anti-inflammatory drugs, hormone replacement therapy or statins.^{44 45}

Alternative hypotheses

A more general concept of dealing with confounding is the use of alternative or competing hypotheses.⁹ An example of an alternative hypothesis is the comparison of different treatments for the same indication.³¹ In **Chapter 3.4**, we argued that the dose-response association between beta-2 agonist use and risk of hip/femur fracture was more likely to reflect the severity of the underlying respiratory disease, instead of a causal relationship. No causal pathway has been described between use of inhaled anticholinergics and risk of hip/fracture. Under the assumption that inhaled anticholinergics and inhaled beta-2 agonists are prescribed for similar indications, we created the alternative hypothesis that we would observe a similar dose-response association between inhaled anticholinergic use and risk of hip/femur fracture. This hypothesis was confirmed in Figure 3.4.2. A similar approach shows similar dose-response associations with fracture risk in users of bronchodilators and ICS respectively, as demonstrated in Table 3.2.2.

Testing the alternative hypothesis that the association between exposure and outcome reflects a causal pathway can be used to evaluate the likelihood of confounding by disease severity and other types of bias. In this thesis, we did not conduct randomised studies. However, pooling the results of the effects of two to three year use of ICS on the risk of vertebral fracture in two RCTs^{46,47} showed a non-significantly increased risk of vertebral fracture, yielding a Mantel-Haenzel odds ratio (OR_{MH})⁴⁸ of 1.68 [95% CI 0.45-6.25]. The limited role of an aetiological pathway is further highlighted after inclusion of preliminary results from the recent

TORCH trial, that resulted in an OR_{MH} of 1.26 [95% CI 0.94-1.70] for the risk of any fracture.⁴⁹

Pooled results from post-hoc analyses of RCTs that were originally designed to assess the efficacy of statins are shown in Figure 2.1.1. The consistent findings of no decreased risk supported the alternative hypothesis that issues in the matching procedure, and not a causal effect of statin use, were a likely explanation for the discrepant reduced risks of fracture in two previously conducted case-control studies that examined the inverse association between the use of statins and the risk of fractures in the same study population (**Chapter 2.1**).⁵⁰ The advantages and disadvantages of involving results from RCTs will now be further discussed.

Historically, randomisation was introduced in clinical trials in order to avoid bias by differential patient allocation. Alternating the treatment allocation, based on the order of inclusion of patients gave biased results because investigators did not strictly adhere to the study protocol.⁵¹ Another advantage of randomisation is the application of statistical theory: an increased sample size will decrease the potential chance of (unknown) differences between the intervention group and its control group.⁵² Although RCTs are generally well-accepted study designs to demonstrate treatment efficacy, they have several limitations. Adverse reactions that occur in one in 1000 patients or less are unlikely to be detected because premarketing drug RCTs usually include 500 to 3000 patients.⁵³ In addition, RCTs often include low-risk patients who have been selected after extensive procedures in which many subjects have been excluded. Moreover, follow-up periods often have a short duration. The resulting problem of limited generalisability (for example to children and elderly who are usually not enrolled in RCTs) can be illustrated with the different baseline risk between RCTs and population-based epidemiological studies. As a result, rate ratios may differ between RCTs and observational research; for example, when comparing the effects of rofecoxib on the risk of acute MI.⁵⁴ Another problem with RCTs can arise when an imbalance between placebo and intervention group occurs during follow-up; for example, due to differential adherence or ad hoc clinical decisions.⁵⁵ Lastly, differences in study design may lead to inconsistent findings between RCTs.

Although RCTs are usually conducted in selected study populations to assess efficacy, the randomisation procedure may be an important advantage compared to (unmeasured) confounding in observational studies, as long as the sample size is sufficiently large. The importance of routine quantitative reporting of adverse events in RCTs was already highlighted 30 years ago.⁵⁶ However, a recent

systematic review of 196 RCTs (in which >4000 subjects were allocated) showed that safety reporting is still largely inadequate. In 58% of these studies, the space of quantitative safety reporting was smaller than or equal to the space for the affiliations of the authors of each study.⁵⁷ Another systematic review demonstrated that there were no substantial differences in relative risk (RR) estimates of harmful effects between RCTs and observational studies. It compared the available intervention and placebo data for 13 different harms from RCTs and non-randomised studies yielding >4000 enrolled patients. However, the clinically more important absolute risk estimates were largely different between both study designs. In addition, the systematic review was limited to adverse events that were reported with a frequency of 1% or more.⁵⁸ In conclusion, meta-analysis of routinely collected adverse events in RCTs can be a useful instrument for the collection of (indirect) evidence of unmeasured biases in epidemiological studies.

Are changes in risk patterns over time in line with the aetiologic pathway?

A general scenario for dealing with immeasurable bias is to examine whether patterns of risk increases over time are in agreement with the expected aetiologic pathway.¹⁰ In this thesis, the large numbers of exposed patients in GPRD and PHARMO RLS allowed us to assess whether observed longitudinal patterns of disease risk from start of exposure would be consistent with the underlying biological mechanism. For example, in **Chapter 2.1** we showed that the risk of fracture was decreased within 30 days of having started the use of statins. This is not consistent with a proposed biological mechanism that is similar to bisphosphonates. Given the biological mechanism, we can specifically argue that it would take at least 6-18 months before statins use could result in a reduced risk of fracture.⁵⁹⁻⁶¹

In the **Chapters 2.2, 3.1, 3.3, 3.4, 4.1 and 4.2** of this thesis, we extended the concept of evaluation of the plausibility of the hypothesised biological mechanism by using smoothing spline plots to visualise the association between recency of exposure, cumulative use, daily dose, and duration of use. The smoothing spline plot is a "best fit curve" commonly used in economics. It is a method of fitting a smooth curve to data as they evolve over time. It has been proposed as an alternative to categorical analysis in epidemiology by Greenland.⁶² In pharmacoepidemiology, smoothing spline analysis has been deployed to study duration of exposure to second and third generation pills and the risk of venous thromboembolism, and

the time since discontinuation of OCs and risk of non-vertebral fracture.^{2,63}

In **Chapter 2.2**, we refuted the hypothesis that the inverse association between use of beta-blockers and risk of hip fracture reflected a causal relationship. This was largely based on a deductive approach: we tested extended hypotheses (the presence of a cumulative dose-response association, a difference between cardioselective and non-cardioselective beta-blockers, and an equal risk among current users with and without a history of exposure to other anti-hypertensive drugs) given the proposed biological mechanism of antagonizing beta-2 receptors on osteoblasts.⁶⁴ As the data did not support any of these extended hypotheses, we did not accept the main hypothesis of beta-blockers reducing the risk of hip fracture. In addition, it seemed unlikely that salbutamol intake would adversely affect the bones, given the blood plasma concentrations of orally administered beta-blockers being about 10.000 times higher than those of inhaled salbutamol. Therefore, our interpretation of no causal effect between use of beta-blockers and risk of hip fracture was used to support the interpretation that confounding by indication partly biased the dose-response association between beta-2 agonist use and risk of hip fracture in **Chapter 3.4**.

The lack of association between respiratory medications and risk of MI after adjustment for disease severity indicators in **Chapters 4.1** and **4.2** supported our hypothesis of confounding by disease severity in epidemiological studies on the risk of ICS use and risk of fracture. Under the assumption that systemic absorption of locally administered respiratory medications did not increase risk of fracture, we created the alternative hypotheses of similar effects on another outcome: acute MI. Given the proposed causal pathways of beta-2 agonists increasing the risk, and ICS reducing the risk of MI, this is an example of indirect support for the hypothesis that the association between use of ICS and risk of fracture does not largely reflect an aetiologic pathway.

Selective prescribing

Despite inverse overall associations between risk of fracture and the use of statins or beta-blockers in **Chapters 2.1** and **2.2**, we demonstrated that changes in risk patterns over time were not consistent with the biological mechanism. Therefore, we considered selective prescribing of statins (related to healthy user bias) or confounding by socioeconomic status (SES) as alternative explanations. Although social deprivation has been associated with lower prescribing rates of statins and with risk of hip fracture,^{65,66} it has not

been highlighted which preferences could explain a GPs' selective prescribing to healthier patients and/or patients with a higher SES.

A survey among 35 General Practitioners (GPs) in the early 90s demonstrated that the high cost of statins may have acted as a prescribing barrier. There was also a moral dimension in the attitude towards the prescribing of lipid-lowering agents. A substantial number of GPs were less likely to treat hyperlipidaemia in obese patients and smokers. They may have considered smoking as a more serious risk factor compared to hyperlipidaemia.⁶⁷ These hypotheses were confirmed in another survey among 26 British GPs: half agreed that lifestyle factors such as smoking, exercise and dietary changes should be addressed before prescribing statins.⁶⁸ Thus, selective underprescribing of statins to smokers and patients with few exercise (risk factors) may have lead to an inverse association between statin use and fracture risk, whereas selective underprescribing to obese patients may have positively biased the risk of hip fracture.^{19 69,70}

Selective underprescribing to smokers may also at least partially explain the 50% reduction in risk of pneumonia in British diabetics who were on statins, as smoking is a risk factor for pneumonia.^{71,72} Furthermore, the doctors' concerns about medicalisation of a patient and his own workload may play a substantial role in the decision to start lipid-lowering or blood pressure-lowering drug treatment.⁶⁸ In **Chapter 2.2**, this may also explain the contrast between our finding of no association between users of beta-blockers without a prior use of antihypertensive drugs and risk of hip fracture, and the 24-27% hip fracture risk reductions in patients who had previously been exposed to other antihypertensive drugs.

Misclassification of exposure and disease

Misclassification of exposure may have occurred because the data in GPRD and PHARMO RLS do not measure the actual use by patients of respiratory medications, especially not the "as needed" use of bronchodilators. However, the misclassification between control patients and patients with fractures (**Chapters 3.2-3.4**) or acute MIs (**Chapters 4.1 & 4.2**) was expected to be non-differential. Given the large numbers of cases and controls and the large study base, even when only 10% of the exposed patients actually took the drug, the resulting shift of the OR towards the null value will be negligible. In addition, exposure misclassification of respiratory medications can be assessed by examining the period shortly after a beta-agonist or ICS dispensing, under the assumption that regular use would be more likely immediately after a dispensing than during subsequent periods.⁷³ Figures 3.3.1 and 3.4.1 clearly show that there

are no substantial differences in fracture risk between the period shortly (e.g. <30 days before the index date) after the most recent dispensing, and longer periods (e.g. one to six months before the index date). In contrast, an increased risk of MI within 30 days before the index date was observed in Figures 4.1.1 and 4.2.1. However, this increased risk may reflect protopathic bias (i.e. symptoms of silent MI, such as dyspnoea and shortness of breath, are related to prescribing of beta-2 agonists and ICS) rather than non-differential misclassification.

Misclassification of the disease may have occurred, depending on the type of outcome. The quality of fracture recording has been validated by review of medical records in GPRD (hip, vertebral) and PHARMO RLS (hip) and appears to be high, i.e. >85-93% of hip fractures could be confirmed.^{2,74} It is unlikely that hip fractures were not recognised by the GP because these patients are usually hospitalised.

In contrast, unrecognised vertebral fractures may have been present in subjects enrolled in GPRD. The recent IMPACT study reported under-diagnosed rates of vertebral fracture that ranged between 30% and 47%.⁷⁵ We can assume that patients with more severe respiratory disease are more likely to be diagnosed because of a higher consultation frequency. This potential protopathic bias may have resulted in an overestimate of the risk of vertebral fracture in **Chapters 3.1** and **3.2**. Prevalence of silent MIs in elderly has been reported to vary between 22 and 68%.⁷⁶ We assume that symptoms of silent MI, like dyspnoea and shortness of breath, are related to prescribing of beta-2 agonists and ICS and may have introduced protopathic bias in **Chapters 4.1** and **4.2**. This may have masked an inverse association between ICS and risk of MI, but it does not explain the lack of association with beta-2 agonists.

5.3 Interpreting evidence for confounding by the severity of the respiratory disease

Observational studies that statistically adjusted for respiratory disease severity

In **Chapter 3.2** and **3.3**, we showed that the dose-response association between ICS use and risk of fracture is at least partially confounded by the severity of the underlying disease in the UK and the Netherlands. These results are in line with observational studies that also extensively adjusted for indicators of the underlying respiratory disease, and found little or no significant association between use of high-dose ICS and risk of fracture. A cohort study among

American elderly enrolled in a health care database reported an OR of 0.93 [95% CI 0.66-1.30] for the association between >840 µg beclomethasone eq./day and risk of non-vertebral fracture.⁷⁷ Similar findings of no increased risk of hip fracture were reported among Canadian elderly (with RRs ranging from 0.92 [95% CI 0.77-1.09] to 1.03 [95% CI 0.66-1.59] for users exposed to 1,000-1,500 µg and >2,000 µg beclomethasone eq./day respectively).⁷⁸ Three studies, including the one in **Chapter 3.2**, have used the GPRD to study the association between use of ICS and risk of fracture. These studies reported a small, non-significantly increased dose-response association.⁷⁹⁻⁸¹ A population-based case-control study in Denmark demonstrated no increased risk of any fracture or hip fracture yielding adjusted ORs of 1.17 [95% CI 1.00-1.38] and 1.13 [95% CI 0.68-1.87] respectively for use of ≥ 600 µg beclomethasone eq./day.^{82a}

Observational studies that minimally adjusted for respiratory disease severity

In addition, the results from the univariate analyses in **Chapter 3.2** and **3.3** (which were not adjusted for the respiratory disease severity) extended the results from two observational studies that only minimally adjusted for indicators of respiratory disease severity. These studies reported an increased risk of fracture. One of these studies, that was conducted in the same GPRD (**Chapter 3.2**), reported an increased risk of hip fracture among users of $\geq 1,600$ µg beclomethasone eq. / day, which is comparable to our results in **Chapter 3.2**.¹² A case-control study nested in a cohort of US veterans with COPD (predominantly males) reported an adjusted OR of 1.68 [95% CI 1.10-2.57] for risk of non-vertebral fracture among users with an average daily dose of 1,616 µg beclomethasone eq./day.^{82b}

Systematic error across observational studies

A potential weakness of a consistent pattern across observational studies is a deficiency that all studies may have in common. All observational studies (including the studies in this thesis), except the study by Vestergaard et al,^{82b} did not adjust for SES. In addition, smoking status and BMI, which were not determined or only partially, could result in confounding in either a positive or a negative direction.

The danger of relying on such a consistent pattern is illustrated by the recent misconception of prevention of cardiovascular disease by HRT. In 1991, a meta-analysis of observational studies by Stampfer et al suggested a 44% reduction of coronary heart dis-

ease (CHD) with HRT. However, the authors did not mention SES as a potential uncontrolled confounder.⁸³ This was a major shortcoming, because already in 1987, Petitti and co-workers observed in an epidemiological study that the inverse association between HRT and cardiovascular mortality was resistant to statistical adjustment. Furthermore, HRT was also associated with a reduced mortality from suicide, homicide and car-accidents. Therefore, the authors suggested that changes in lifestyle may have explained their results.⁸⁴ One decade after the meta-analysis by Stampfer et al, the large Women's Health Initiative RCT showed that HRT did not protect against CHD.⁸⁵ Finally, a new meta-analysis of observational studies refuted the causal hypothesis of HRT-induced heart-protection by evaluating the competing hypothesis that SES may have confounded the inverse association between HRT and CHD.⁸⁶

Disease or drugs?

In **Chapter 3.2** and **3.3** it was shown that the dose-response association between ICS use and fracture risk substantially decreased after adjustment for indicators of disease severity. However, there was still a dose-response trend, as shown in Table 3.2.2 and Figure 3.3.3. The remaining increased association may be partially explained by residual confounding of disease severity. However, we cannot exclude a -small- causal effect of ICS.

Although it is currently not possible to quantitatively estimate an OC-induced risk of fracture due to a certain BMD change,⁸⁷ several RCTs have reported small decreases in BMD after 2-3 years of ICS exposure (~ 400-800 µg/day). The BMD changes have been pooled and analysed in two systematic reviews. A Cochrane review did not report any significant changes with ICS therapy, whereas a review that was conducted by the World Health Organisation (WHO) found that ICS use significantly reduced lumbar spine and femoral neck BMD.^{88,89} This difference could be due to the Cochrane review not including the Lung Health Study (LHS) in its systematic literature search.^{35,88} The LHS demonstrated relatively large BMD reductions after 3 years of ICS treatment and excluding this study resulted not only in an increase in the confidence interval of the pooled BMD estimate, but also shifted the pooled estimate towards the null value which ultimately led to the interpretation of no increased risk.

As expected, adjustment for indicators of confounding by respiratory disease severity did not only result in substantial decreases of the association between hip fracture risk and ICS (**Chapter 3.2** and **3.3**), but also with beta-2 agonists (**Chapter 3.4**). Our

interpretation of no causal relationship between beta-blocker use and fracture risk (**Chapter 2**) supported the use of daily dose of beta-2 agonists as a proxy for respiratory disease severity. Furthermore, the excess risk in the association between respiratory medications and MI also substantially decreased after adjustment for disease severity. Moreover, there were no differences among use of ICS, beta-2 agonists and inhaled anticholinergics and the risk of fracture (Figure 3.4.2). **Chapters 4.1** and **4.2** supported the limited role of systemic absorption of ICS and beta-2 agonists. Our adjusted results of ICS use and fracture risk are in line with other observational studies that adjusted for indicators of the severity of the underlying respiratory disease; furthermore, our unadjusted results are also in keeping with other observational studies that minimally adjusted for indicators of the severity of the underlying respiratory disease. Moreover, RCTs have shown a decreased BMD after two to three years of ICS exposure, but it cannot be quantified to which extent this reduced BMD has attributed to the increased risk of fracture in epidemiological studies. In conclusion, there is accumulating evidence that it is likely that the association between use of ICS and risk of hip fracture is largely confounded by the severity of the underlying respiratory disease.

5.4 Clinical implications

Our studies have two clinical implications. First, regardless of the underlying cause, we have shown that elderly users of high dosages of ICS are at increased risk of fracture. Fracture risk assessment may be indicated among users of high dosages ($>1,600$ μg beclomethasone eq./day) of ICS (**Chapters 3.2** and **3.3**). Second, cardiovascular risk assessment should be considered in users of ICS, beta-2 agonists and antihypertensive medication when suffering from ischaemic heart disease (**Chapters 4.1** and **4.2**).

Methodological implications

Our studies have several methodological implications. We have shown that evaluation of confounding by the severity of respiratory disease can be approached by deductively testing a variety of causal, competing and auxiliary hypotheses. Furthermore, the use of smoothing spline visualisations in the study of large healthcare databases can be an informative instrument to determine whether the observed hazard function is in line with the expected underlying biological mechanism. Finally, showing the results of sensitivity analyses are highly recommended, especially when unintended beneficial effects in selected study populations are found.

5.5 Final considerations

What are the next challenges? First, future improvement of the determination of respiratory disease severity in large healthcare databases can be expected. For example, under the UK Quality and Outcomes Framework, GPs are rewarded for spirometry or peak flow measurement in patients with asthma/COPD since April 2003.⁹⁰ Second, meta-analysis of adverse events in RCTs may inform us on immeasurable bias in non-randomised drug safety studies. Third, in large healthcare databases, spline visualisations have shown to be useful instruments in order to determine whether patterns of risk changes over time in an epidemiological study is in line with the underlying biological mechanism, or whether (unmeasured) confounding or bias is reflected. Fourth, we need to better understand which individuals with respiratory disease are particularly at increased risk of fracture or MI. Further elucidation of the underlying mechanism of local and systemic inflammation in patients with obstructive airway disease may be helpful.

Unmeasured systematic differences between medication users and the comparison group across multiple, similar observational studies are a potential pitfall for pharmaco-epidemiology and its credibility towards the prescribers and users of the medication. Therefore, it has even been suggested to “restrict observational studies to research questions that can meet the underlying assumption that exposure allocation is unrelated to the outcome”.⁵² Alternatively, the controversies and variability in results in epidemiological research can be approached as challenging opportunities for what Lewis Sheiner has called “learning” in the “learn-confirm” cycle of drug development.⁹⁰ A commentary on **Chapter 2.1** has expressed this challenge as follows: “We still need observational studies of drugs - they just need to be better.”⁹¹

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Appendices

Summary

Inhaled corticosteroids (ICS) are drugs that are commonly prescribed for the treatment of asthma and Chronic Obstructive Pulmonary Disease (COPD). Although the systemic absorption is lower than that of oral corticosteroids (OCs), there have been concerns of adverse effects like osteoporosis and risk of fracture. In 2002, an epidemiological study showed a dose-dependent association between use of ICS and the risk of hip fracture. More recent studies have suggested that the severity of the underlying respiratory disease may also result in a decreased bone mineral density, regardless of the use of OCs or ICS. This suggests that severity of the underlying respiratory disease may be an important confounder of the association between use of ICS and risk of hip fracture. Due to its multifactorial nature and measurement difficulties, the determination of such bias is a major challenge in the epidemiological studies. The scope of this thesis was to evaluate the extent of confounding by respiratory disease in patients using ICS. The main outcome in this thesis was that of fractures. Myocardial infarction was another outcome that was evaluated in order to distinguish between a drug related and a disease related effect of ICS. The hypothesis was that any systemic absorption of ICS may affect the risk of myocardial infarction in addition to that of fracture.

Methodological topics of the study of large health care databases are discussed in **Chapter 2**. In 2000 and 2001, two independently conducted case-control studies reported contrasting results on a possible beneficial effect of the use of statins on the risk of fracture. The findings were remarkable, because both studies had been conducted in the same study population, the UK General Practice Research Database (GPRD). In **Chapter 2.1**, we reanalyzed both original study designs (a “selected-population” and an “population-based or entire population” design) and we addressed a variety of hypotheses that were proposed in the debate that had followed the two original publications. We found a substantial difference in fracture risks with the two different study designs. However, this difference reduced after matching case and control patients by the same year of birth, instead of matching by five-year age bands. In addition, the exposure time-window, the selection of confounders and exclusion of high-risk patients before matching influenced the results. Furthermore, the results indicated that there was a 50% reduction of fracture risk after only one statin prescription. This suggests that the inverse association between statin use and hip fracture in GPRD may not reflect a causal effect, but rather the presence of bias and confounding. **Chapter 2.1** was the first

epidemiological study suggesting that broad matching criteria for age should be avoided in case-control studies.

The discovery that beta-2 receptors are present on osteoblasts and reports that the adrenergic pathway is involved in bone remodeling in rodents support beneficial effects of beta-blockers on the risk of hip fracture. Therefore, we tested this hypothesis in two case-control studies in **Chapter 2.2**. Although we found that current beta-blocker reduced the risk of hip fracture in GPRD by 18%, and in the Dutch PHARMO-Record Linkage System by 13%, the real challenge of this study was to determine to which extent the decreased associations reflected a causal relationship or unknown distortion. None of our analyses supported a biological mechanism: we did not observe a cumulative dose-response association, and stratification to beta-blocker selectivity did not result in stronger effects for non-cardioselective beta-blockers, as would be expected. Finally, we found that the protective effect was only present in patients with a history of using other antihypertensive drugs, which is not in keeping with the hypothesised biological mechanism. Thus, our results suggest that the observed inverse association between use of beta-blockers and risk of hip fracture does not reflect a causal relationship.

In **Chapter 3.1**, we evaluated the risk of fracture among users of intermittent high-dose OCs in GPRD. The effects of continuous, low-dose OC use on risk of fracture have been well established. In contrast, the effects of high doses intermittent regimens on risk of fracture have not yet been evaluated. We showed that increasing cumulative exposure to OCs resulted in a substantially increased risk of fracture in users of high dose OCs (≥ 15 mg/day), whereas high dose users with a low cumulative exposure (less than one gram prednisone equivalents) had only a small increased risk of fracture. Moreover, the fracture risk returned to baseline six months after cessation of high dose OCs. These results suggest that high dose oral OC users (≥ 15 mg prednisone equivalents/day and a cumulative exposure of more than one gram) have substantially increased risks of fracture. Further investigations and preventative treatment might be conveniently targeted to these patients.

Chapter 3.2 describes a direct approach for the evaluation of confounding by respiratory disease severity in the association between use of ICS and risk of osteoporotic fractures. Using the same study population, the GPRD, we were able to mimic the results of a previously reported dose-response association between ICS use and risk of hip fracture, with a 1.8-fold increased risk of hip fracture among patients who had been exposed to $\geq 1,600$ μg beclomethasone equivalents/day. We identified several indicators for

the severity of the underlying respiratory disease, including the exposure to bronchodilators. Adjustments for these indicators resulted in a substantive decrease of the magnitude of this dose-response association, yielding a non-significantly 1.2-fold increased risk of fracture among users of $\geq 1,600$ μg beclomethasone equivalents/day. We found similar results for the risk of osteoporotic and vertebral fractures. These results support the hypothesis that confounding by severity of underlying diseases explains most of the excess risk of fracture in ICS users.

In **Chapter 3.3**, we evaluated the same concept of confounding by the severity of the underlying respiratory disease in the Dutch PHARMO RLS database. In this study, we focused on the risk of hip fracture and subsequently evaluated the effect of indicators of confounding by the underlying inflammatory disease in the dose-response association between oral OC use and risk of hip fracture. We found dose-response associations between use of OCs or ICS and the risk of hip fracture. After adjustment for the severity of the underlying respiratory disease or inflammatory disease, the excess risk mostly disappeared among users of ICS, whereas the risk of hip fracture remained elevated among users of high doses of OCs. In conclusion, our findings suggest that ICS use is not an independent risk factor for hip fracture risk. In contrast, oral OC use was associated with an increased risk of hip fracture that was only partly explained by the underlying disease severity.

Recent findings that beta-2 agonists decreased bone mineral density in rodents has been the rationale for the study in **Chapter 3.4**. We evaluated the possibility that use of beta-2 agonists could increase the risk of hip fracture in humans, due to systemic absorption. We demonstrated a 1.4-fold increased risk of hip fracture among beta-2 agonist users. However, the excess risk disappeared after adjustment for indicators of the severity of the underlying disease. High dose beta-2 agonist use ($>1,600$ μg salbutamol equivalents/day) was associated with a crude two-fold increased risk of hip fracture, which was comparable to that of high dose ICS. In addition, we observed a $\sim 50\%$ decrease in the daily dose-response association between beta-2 agonist use and hip fracture risk after adjustment for respiratory disease severity. The remaining dose response association was almost identical to the relationships between inhaled anticholinergics and risk of hip fracture. Likewise, in an oral OC-naïve study population, the excess fracture risk substantially decreased, with a remaining non-significantly 1.3-fold increased risk of hip fracture among users of $>1,600$ μg salbutamol equivalents/day. Therefore, our results suggest that the severity of the underlying respiratory disease, rather than the use of beta-2

agonists may play an important role in the aetiology of hip fractures in patients using beta-2 agonists.

Beta-2 agonists have a long history of possible associations with cardiovascular morbidity and mortality. In **Chapter 4.1**, we evaluated the association between the use of beta-2 agonists and the risk of non-fatal acute myocardial infarction (MI) in a high-risk population (users of antihypertensive drugs). We found that use of beta-2 agonists was no longer associated with an increased risk of acute MI after adjustment for respiratory disease severity. In contrast, we demonstrated that the risk was a two-fold increased in beta-2 agonist users with a history of ischaemic heart disease. It was also found that patients who had recently started beta-2 agonists were also at increased risk of MI. We explained our results by protopathic bias: dyspnea-like symptoms of unrecognised, latent ischaemic heart disease were treated with beta-2 agonists, which may explain this association among recent starters. It was concluded that cardiovascular risk assessment should be considered in users of beta-2 agonists and antihypertensive drugs, when suffering from ischaemic heart disease.

In patients with COPD, a 50% decrease of plasma levels of the inflammatory marker C-reactive protein after two weeks of exposure to ICS has been reported. As a result, it has been speculated that ICS may therefore reduce the risk of MIs through a biological pathway that is similar to statins. In **Chapter 4.2** we tested the hypothesis of an inverse association between use of ICS and risk of non-fatal MI in a high-risk population. We did not find an association between use of ICS and risk of acute MI after adjustment for the severity of the underlying respiratory disease. In the light of the suggested pharmacological mechanism, we would have expected reductions of MI with a higher daily dose and a longer duration of use. However, our results did not support any of these hypotheses. In contrast to a beneficial effect, we found a non-significantly 1.9-fold elevated risk of MI among users of >1,600 µg beclomethasone equivalents/day. In conclusion, our results do not support the hypothesis that ICS may protect against risk of acute MI by the reduction of C-reactive protein.

Chapter 5 provides a general discussion. First, we have shown the methodological strategy for determining confounding by the severity of the respiratory disease in the association between the use of ICS and the risk of fracture. The strategy consisted of several approaches. We directly adjusted our analysis for confounder indicators of the severity of the underlying respiratory disease. In addition to statistical adjustment, in each study, we have designed several auxiliary analyses that could indirectly show us whether our re-

sults were in line with a hypothesised biologically plausible causal pathway. The use of smoothing spline analysis has shown to be a useful instrument in order to graphically visualise deviations from hypothesised hazard functions. Furthermore, we have shown how the findings from **Chapter 2.2** (beta-blocker use and hip fracture risk) supported interpretation of the results in **Chapter 3.4** (beta-2 agonists use and hip fracture risk). The findings in this chapter suggested that beta-2 agonist use could be used as a proxy for the severity of the underlying respiratory disease in **Chapters 3.2 and 3.3**. Another example of indirectly testing of the hypothesis that systemic absorption of ICS and beta-2 agonists was unlikely to result in side effects was shown in **Chapters 4.1 and 4.2**. In general, this thesis is an example of a methodological approach that uses a variety of alternative hypotheses in order to determine the presence of confounding by respiratory disease severity in the association between the use of ICS and the risk of fracture.

Samenvatting

Inhalatiecorticosteroïden zijn ontstekingsremmende geneesmiddelen die worden voorgeschreven aan patiënten met astma of COPD.

Astma is een aandoening waarbij sprake is van luchtwegen die bijzonder prikkelbaar zijn. Inademing van prikkelende stoffen kan leiden tot het uitlokken van klachten zoals benauwdheid, hoesten of een piepende ademhaling. In Nederland lijdt meer dan 6% van de Nederlandse bevolking aan astma. COPD is een chronische aandoening aan de luchtwegen waarbij het ademen is bemoeilijkt. De belangrijkste aandoeningen die tot COPD worden gerekend zijn chronische bronchitis en emfyseem. De beginfase van COPD kenmerkt zich door toegenomen slijmvorming in de luchtwegen, en hoesten. In een later stadium raken de structuur van de longen beschadigd en neemt de longinhoud af. Kortademigheid is vaak het resultaat. In Nederland lijdt naar schatting 4% van de bevolking aan COPD. Dit zijn overwegend patiënten van 45 jaar en ouder (bron: www.astmafonds.nl).

Inhalatiecorticosteroïden worden door astmapatiënten gebruikt om ontsteking van de luchtwegen te verminderen, en klachten te voorkomen. De rol van inhalatiecorticosteroïden in de behandeling van COPD is minder duidelijk. Mogelijk vermindert het gebruik van inhalatiecorticosteroïden de kans op aanvallen van benauwdheid. Bovendien zeggen gebruikers van deze geneesmiddelen een betere kwaliteit van leven te hebben. In 1998 bleek zo'n 60% van de Nederlandse bevolking met COPD inhalatiecorticosteroïden te gebruiken. Naast inhalatiecorticosteroïden kunnen patiënten met astma of COPD worden behandeld met luchtwegverwijders. Deze geneesmiddelen worden ook geïnhaleerd, en zorgen voor een snelle verwijding van de luchtwegen, waardoor het gevoel van benauwdheid vermindert.

Osteoporose (botontkalking) is een ziekte waarbij de botten zo poreus worden, dat ze gemakkelijk breken. In Nederland breken jaarlijks ruim 83.000 mensen boven de 55 jaar een of meerdere botten ten gevolge van osteoporose. De belangrijkste botbreuken zijn die van de heup (15.000 mensen) en een inzakking van de wervelkolom (16.000 mensen). Een ingezakte wervelkolom veroorzaakt doorgaans veel chronische pijn. De gevolgen van een gebroken heup zijn over het algemeen ernstiger: het aantal mensen dat een jaar na de heupfractuur is overleden wordt geschat op 18%. De helft van de patiënten die zijn heupfractuur overleeft, kan na een periode van revalidatie de niet meer zelfstandig lopen. Het identificeren van risicofactoren voor het krijgen van osteoporotische botbreuken is dus be-

langrijk. Hierdoor zou een deel van deze botbreuken kunnen worden voorkomen.

In 2002 werd in twee farmacoepidemiologische studies gesuggereerd dat het gebruik van hoge doses inhalatiecorticosteroiden zou leiden tot botontkalking of heupfracturen. Als er een verband zou bestaan tussen het gebruik van hoge doses inhalatiecorticosteroiden en botbreuken, dan zou dit ertoe kunnen leiden dat aan patiënten met astma/COPD minder snel hoge doses inhalatiecorticosteroiden zouden worden voorschreven, of dat het aantal geneesmiddelen waarmee hun luchtwegklachten kan worden behandeld, zou worden beperkt.

Inmiddels is ook onderzoek gepubliceerd waarin werd gesuggereerd dat de ernst van de onderliggende luchtwegaandoening wellicht bijdraagt aan botontkalking. Dit proefschrift draait daarom om de vraag of het verhoogde risico van botbreuken een gevolg is van het gebruik van ontstekingsremmers (de inhalatiecorticosteroiden) of de ernst van de onderliggende luchtwegziekte.

In **Hoofdstuk 2** worden de resultaten van twee methodologische onderzoeken besproken. In 2000 en 2001 zijn twee epidemiologische onderzoeken gepubliceerd die verschillende conclusies trokken over een mogelijk beschermend effect van statines (cholesterolverlagende geneesmiddelen) op het krijgen van botbreuken. Dit was opmerkelijk omdat beide onderzoeksgroepen dezelfde database hadden bestudeerd, de Britse “General Practice Research Database” (GPRD). Net als in Nederland vervult de huisarts in Groot-Brittannië de functie van poortwachter tot de gezondheidszorg. Bovendien registreert hij het overgrote deel van de recepten van medisch specialisten. De GPRD bevat gegevens over voorgeschreven medicatie, diagnoses en symptomen, laboratoriumuitslagen, ziekenhuisopnames en -ontslagen, en “life-style” parameters zoals rookgedrag, lengte en gewicht van ongeveer acht miljoen inwoners van het Verenigd Koninkrijk. In **Hoofdstuk 2.1** wordt beschreven hoe de oorzaak van dit verschil is onderzocht door de eerdere onderzoeken te herhalen. De belangrijkste oorzaken voor de verschillende resultaten betroffen onder meer de selectie-procedure van de controlepatiënten (“matching”) en de statistische correctie van de resultaten. Daarnaast speelde de lengte van de tijdsperiode waarin het gebruik van de cholesterolverlagers werd bepaald een grote rol.

Tot het begin van deze eeuw dacht men dat het continue proces van botopbouw en -afbraak overwegend werd gereguleerd door hormonen. De ontdekking van zogenaamde bèta-2 receptoren op botcellen leidde tot de veronderstelling dat osteoporose mogelijk kon worden voorkomen door geneesmiddelen die deze bèta-2 re-

ceptoren blokkeren, de zogenaamde bètablokkers. Dit is een groep geneesmiddelen die in 2005 door meer dan 1,3 miljoen Nederlanders werd gebruikt, hoofdzakelijk om de bloeddruk te verlagen. In **Hoofdstuk 2.2** hebben we deze veronderstelling getest door in twee databases met patiëntgegevens te kijken of bètablokkers de kans op heupfracturen verminderen in het Verenigd Koninkrijk en Nederland. Hoewel het gebruik van bètablokkers was geassocieerd met een 18% en een 13% verlaging van het aantal heupfracturen in respectievelijk het Verenigd Koninkrijk en Nederland, leek dit geen causaal verband te weerspiegelen. Onze aanvullende veronderstellingen (een verband tussen de cumulatieve blootstelling en een verder beschermend effect, een verschil tussen cardioselectieve en niet-cardioselectieve bètablokkers) werden niet ondersteund door de resultaten. Ten slotte vonden we dat het beschermende effect van bètablokkers alleen aanwezig was in een groep patiënten met een voorgeschiedenis van bloeddrukverlagende geneesmiddelen. Ook deze waarneming ondersteunde geen biologisch oorzakelijk verband, en daarom concludeerden we dat gebruik van bètablokkers waarschijnlijk niet beschermt tegen het krijgen van botbreuken.

Hoofdstuk 3.1 is het eerste onderzoek dat de kans op botbreuken bepaalde in patiënten die stootkuren orale corticosteroiden toegediend krijgen. Orale corticosteroiden (bijvoorbeeld prednison) zijn net als inhalatiecorticosteroiden ontstekingsremmende geneesmiddelen. Ze kunnen voorgeschreven worden bij een groot aantal aandoeningen waarbij ontstekingen een belangrijke rol spelen. De belangrijkste zijn luchtwegaandoeningen, reumatoïde artritis en inflammatoire darmziekten (de ziekte van Crohn en Colitis Ulcerosa). Eerder werk van onze groep heeft laten zien dat continu gebruik van laaggedoseerde orale corticosteroiden zoals prednison kan leiden tot een verhoogde kans op botbreuken. In dit onderzoek hebben we laten zien dat bij patiënten die een hoge dagdosis slikken (≥ 15 mg prednison equivalent per dag), de kans op fracturen wordt vergroot bij een toegenomen cumulatieve blootstelling, in het bijzonder na gebruik van één gram in een tijdsperiode waarbij de periodes tussen stootkuren niet langer duurden dan drie maanden.

In **Hoofdstuk 3.2** wordt een directe aanpak beschreven om de rol van de ernst van onderliggende luchtwegziekte in de associatie tussen inhalatiecorticosteroiden en de kans op osteoporotische botbreuken te bepalen. We konden een eerder beschreven dosis-response associatie tussen het gebruik van inhalatiecorticosteroiden en heupfracturen in de Britse “General Practice Research Database” reproduceren. Oudere patiënten die een hoge dosis ($\geq 1,600$ µg beclomethason equivalent per dag) inhaleerden, leken een bijna verdubbeld risico te lopen om hun heup te breken. Na statistische cor-

rectie voor indicatoren van de ernst van de onderliggende ziekte (inclusief de blootstelling aan luchtwegverwijders), bleek het verhoogde risico vrijwel verdwenen te zijn. Een grote afname in het verhoogde fractuurrisico werd gevonden voor de kans op andere type botbreuken. Deze bevindingen ondersteunen de hypothese dat het verband tussen de dagdosering van inhalatiecorticosteroiden en de kans op botbreuken wordt vertekend door de ernst van de onderliggende luchtwegaandoening.

In **Hoofdstuk 3.3** is een onderzoek uitgevoerd dat vergelijkbaar is met dat in **Hoofdstuk 3.2**. Echter, er is hier gebruik gemaakt van patiëntgegevens uit de Nederlandse PHARMO RLS database, en ook is duidelijker ingegaan op de relatie tussen de dagdosering van orale corticosteroiden en de kans op botbreuken van de heup. Ook deze studie ondersteunde de veronderstelling dat het verband tussen de dagdosering van inhalatiecorticosteroiden en de kans op botbreuken wordt vertekend door de ernst van de onderliggende luchtwegaandoening.

Bèta-2 agonisten zijn een groep geneesmiddelen die na inhalatie de luchtwegen direct verwijderen. Dit gebeurt doordat deze geneesmiddelen door middel van een soort sleutel-slot systeem aangrijpen op bèta-2 receptoren die aanwezig zijn in de luchtwegen. In **Hoofdstuk 2.2** is reeds beschreven dat we sinds enkele jaren weten dat deze bèta-2 receptoren zich ook op cellen bevinden die betrokken zijn bij de botopbouw en -afbraak. Stimulering van deze bèta-2 receptoren door een bèta-2 agonist heeft in knaagdieren geleid tot een verlaagde botdichtheid. Hoewel bèta-2 agonisten worden geïnhaleerd via de longen, komt een deel van deze geneesmiddelen terecht in de bloedbaan. In **Hoofdstuk 3.4** is daarom voor het eerst onderzocht of bèta-2 agonisten de kans op heupfracturen in mensen mogelijk verhogen. We hebben dit gedaan door een epidemiologische studie uit te voeren in de Nederlandse PHARMO RLS database. We vonden een verhoogd risico van heupbreuken bij patiënten die bèta-2 agonisten gebruikten. Dit risico was zelfs verdubbeld bij patiënten die zeer hoge doses ($\geq 1,600$ µg salbutamol equivalent per dag) bèta-2 agonisten inhaleerden. Uiteindelijk bleek dat dit verhoogde risico niet door de bèta-2 agonisten zelf, door de ernst van de onderliggende ziekte en het gelijktijdig gebruik van orale corticosteroiden kon worden verklaard.

In **Hoofdstuk 4.1** is het verband tussen het gebruik van bèta-2 agonisten en het risico van een niet-fataal hartinfarct onderzocht. Dit is gedaan binnen een groep Nederlanders die bloeddrukverlagende geneesmiddelen gebruiken. Nadat we statistisch hadden gecorrigeerd voor de ernst van de onderliggende luchtwegziekte, bleek dat het gebruik van bèta-2 agonisten niet meer was geassocie-

eerd met een verhoogde kans op hartinfarcten. Echter, binnen een groep patiënten met ischaemische hartklachten, leek het gebruik van bèta-2 agonisten de kans op een hartinfarct te verdubbelen. Dit risico was ook verhoogd in patiënten die kortdurend deze ischaemische hartklachten hadden. Omdat symptomen zoals kortademigheid zowel het gevolg kunnen zijn van een luchtwegaandoening, als een voorbode kunnen zijn van een hartinfarct, veronderstelden we dat er wellicht geen sprake was van een oorzakelijk verband tussen het gebruik van bèta-2 agonisten en hartinfarcten. Wanneer artsen luchtwegmedicatie voorschrijven aan patiënten die bloeddrukverlagers gebruiken en leiden aan ischaemische hartziekte, is het belangrijk dat zij rekening houden met de mogelijkheid van voortekenen een hartinfarct.

Bij patiënten met COPD is beschreven dat inhalatiecorticosteroiden na twee weken gebruik de chronische ontsteking in het lichaam met de helft kunnen verlagen. Het gegeven dat statines, een groep cholesterolverlagende geneesmiddelen, dit op vergelijkbare wijze doen, heeft geleid tot de veronderstelling inhalatiecorticosteroiden zouden kunnen beschermen tegen het krijgen van een hartinfarct. In **Hoofdstuk 4.2** hebben we dit onderzocht in de Nederlandse PHARMO RLS database. We vonden geen omgekeerde relatie tussen het gebruik van inhalatiecorticosteroiden en de kans op het krijgen van een hartinfarct. Ook na gebruik van hogere doses of een langere gebruiksduur trad dit effect niet op. Onze resultaten ondersteunen niet de veronderstelling dat inhalatiecorticosteroiden beschermen tegen het krijgen van een hartinfarct.

Hoofdstuk 5 bevat een algemene discussie over dit proefschrift. Er is een algemene aanpak beschreven hoe de ernst van de ziekte in kaart kan worden gebracht als factor die de relatie tussen gebruik van inhalatiecorticosteroiden de kans op botbreuken vertekent. Als eerste is direct statistisch gecorrigeerd voor een aantal indicatoren van de ernst van de onderliggende luchtwegaandoening. Deze statistische aanpassing is vervolgens uitgebreid met aanvullende veronderstellingen die getest konden worden. Het gebruik van “smoothing spline” analyses bleek een nuttig meetinstrument om de biologische plausibiliteit van de veronderstellingen verder te onderzoeken.

Dit proefschrift is een voorbeeld van een algemene methodologische aanpak, om via verschillende directe en indirecte benaderingen te onderzoeken of het gebruik van inhalatiecorticosteroiden de kans op botbreuken verhoogt. De conclusie op basis van deze aanpak, en op basis van resultaten uit andere onderzoeken, is dat patiënten die hoge doses inhalatiecorticosteroiden gebruiken, waarschijnlijk een verhoogde kans op botbreuken hebben. Dit komt

wellicht niet door het middel zelf, maar in grote mate door de ernst van de onderliggende luchtwegaandoening. Een verandering in het gebruik van luchtwegmedicatie in deze groep patiënten is daarom waarschijnlijk niet nodig.

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List of publications

[Articles marked with an asterix (*) relate to the work described in this thesis. Articles marked with a cross (†) relate to original research.]

- † Van Staa TP, Wegman S, **de Vries F**, Leufkens B, Cooper C. Use of statins and risk of fractures. *JAMA* 2001;285:1850-5.
- Van Staa TP, Wegman S, **de Vries F**, Leufkens B, Cooper C. Statins and fracture risk. *JAMA* 2001;286:669-70.
- De Vries F**, Vermes A, Vulto AG. Geneesmiddelprofiel Fomepizol (Opi ®) [Article in Dutch]. *Pharm Weekbl* 2003;138:37-41.
- De Vries F**, Kruik-Kollöffel WJ. Influenzavaccinatie tijdens behandeling met cytostatica. Verminderde afweer en immuunrespons [Article in Dutch]. *Pharm Weekbl* 2003;138:658-663.
- *† **De Vries F**, van Staa TP, Bracke M, Leufkens HGM, Cooper C, Lammers J-WJ Severity of obstructive airway disease and risk of osteoporotic fractures. *Eur Respir J* 2005; 25:879-884.
- *† **De Vries F**, van Staa TP, Bracke M, Leufkens HGM, Cooper C, Lammers J-WJ Sterke obstructie luchtwegen verhoogt fractuurrisico [Article in Dutch]. *Pharm Weekbl* 2005;140:744-747.
- Van Staa TP, **de Vries F**, Leufkens HGM. Gastric acid-suppressive agents and risk of Clostridium difficile-associated disease. *JAMA* 2006;295:2599.
- *† **De Vries F**, Pouwels S, Bracke M, Leufkens HGM, Cooper C, Lammers J-WJ, van Staa TP. Use of beta-2 agonists and risk of hip/femur fracture: a population-based case-control study. *Pharmacoepidemiol Drug Saf* (in press).
- *† **De Vries F**, de Vries CS, Cooper C, Leufkens HGM, van Staa TP. Reanalysis of two studies with contrasting results on the association between statin use and fracture risk: the General Practice Research Database. *Int J Epidemiol*. 2006;35(5):1301-8.
- *† **De Vries F**, Bracke M, Leufkens HGM, Lammers J-WJ, Cooper C, van Staa TP. Fracture risk with intermittent high-dose oral glucocorticoid therapy. *Arthritis Rheum* (in press).
- *† **De Vries F**, Souverein P, Cooper C, Leufkens HGM, van Staa TP. Use of beta-blockers and the risk of hip/femur fracture in the United Kingdom and the Netherlands. *Calcif Tissue Int* (in press).
- *† **De Vries F**, Pouwels S, Lammers J-WJ, Leufkens HGM, Bracke M, Cooper C, van Staa TP. Use of inhaled and oral glucocorticoids, severity of inflammatory disease and risk of hip/femur fracture: a population-based case-control study. *J Intern Med* (in press).
- † Wilting I, **de Vries F**, Thio BMKS, Cooper C, Heerdink ER, Leufkens HGM, Nolen W, Egberts ACG, van Staa TP. Lithium use and risk of fractures. *Bone* (in press).
- *† **De Vries F**, Pouwels S, Bracke M, Lammers J-WJ, Klungel OH, Leufkens HGM, van Staa TP. Evidence for no association between use of beta-2 agonists and risk of acute myocardial infarction in patients with hypertension. (Submitted).
- *† **De Vries F**, Pouwels S, Bracke M, Lammers J-WJ, Klungel OH, Leufkens HGM, van Staa TP. Use of inhaled corticosteroids and the risk of non-fatal acute myocardial infarction. (Submitted).

Curriculum vitae

Frank de Vries was born in Groningen, The Netherlands on 17 January 1977. He studied pharmaceutical sciences at “Universiteit Utrecht”, the Netherlands and was awarded his Doctor of Pharmacy degree in 2002. In the same year, he accepted his first position as a Ph.D. student at the Utrecht Institute for Pharmaceutical Sciences. Frank initiated various drug safety studies, which are included in the current thesis. During his Ph.D. research fellowship, Frank worked as a pharmacist in the “Jordaan apotheek” in Amsterdam.

In 2004, the work for his publication “severity of obstructive airway disease and risk of osteoporotic fracture” (**Chapter 3.3**) was awarded by the International Society for Pharmacoepidemiology (ISPE), the British National Osteoporosis Society (NOS), and the American Society for Bone and Mineral Research (ASBMR). In the same year, Frank accepted a temporary position as a visiting researcher at the Postgraduate Medical School, University of Surrey, Guildford, United Kingdom. In 2005, he received a “young investigator’s award” at the European Calcified Tissue Society /International Bone and Mineral Society meeting in Geneva for his work on beta-blocker use and risk of fracture (**Chapter 2.2**). Frank’s computer programming skills were acknowledged by the SAS Institute EMEA HQ (www.sas.com), which invited him to become a “SAS Student Ambassador” in 2006. In the same year, he reviewed manuscripts for “Osteoporosis International” and the “American Journal of Respiratory and Critical Care Medicine”.

From January 2007, Frank has been conducting epidemiological studies working as an independent consultant (www.fdevries.com). In the same period, he has been continuing his academic work as a researcher at the Utrecht Institute for Pharmaceutical Sciences, Universiteit Utrecht, Netherlands.

