Patients at increased fracture risk: identification and pharmacological treatment

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Patients at increased fracture risk: identification and pharmacological treatment

Patiënten met een verhoogd risico op botbreuken:
identificatie en farmacologische behandeling
(met een samenvatting in het Nederlands)

Proefschrift

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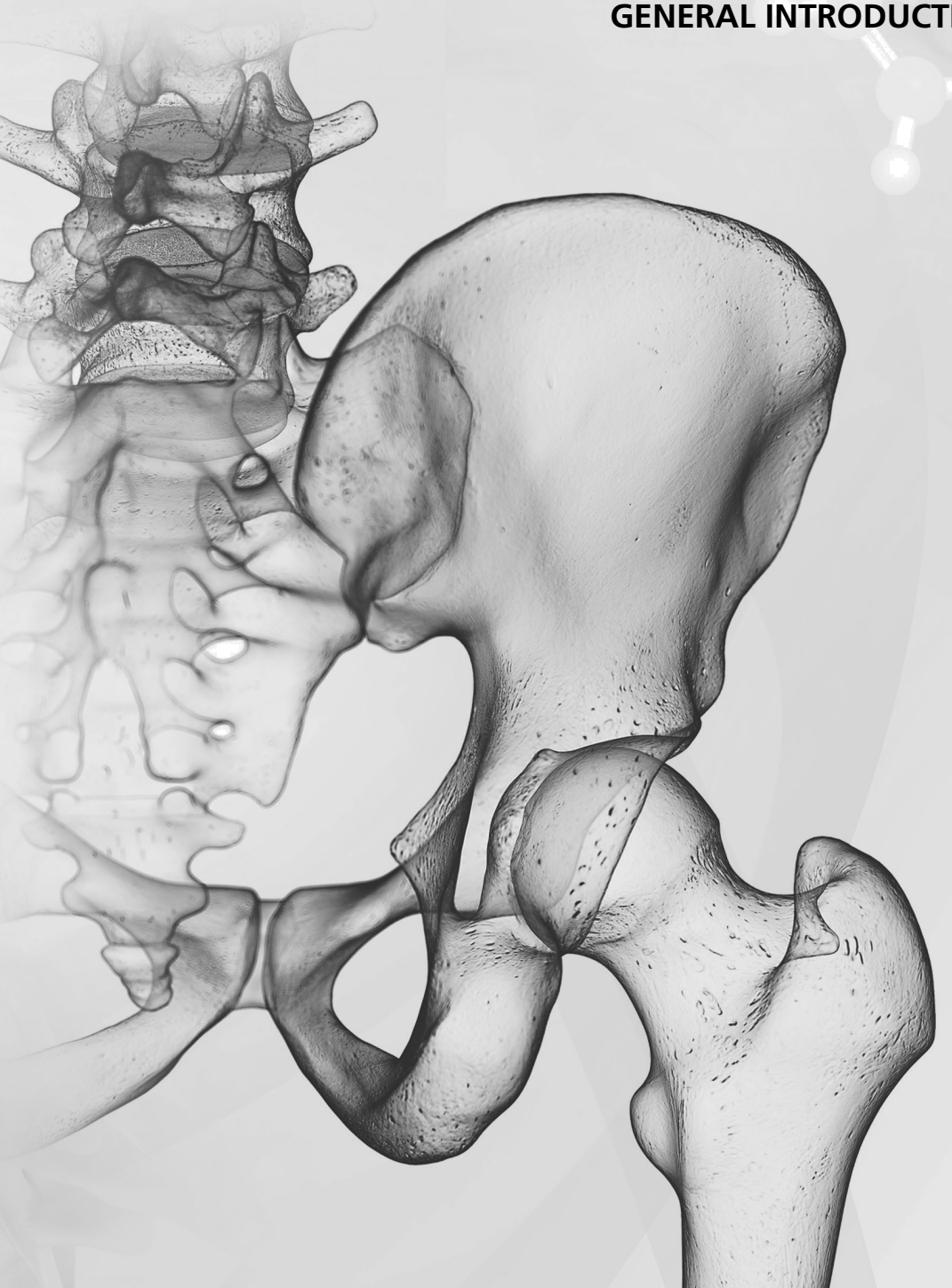
CHAPTER 1

GENERAL INTRODUCTION



FRACTURE BURDEN

Fragility fractures are common and are associated with a substantial burden for patients and the healthcare system. They typically result from low-energy trauma such as a fall from standing height and are most frequent at the hip, forearm, spine, and humerus but they can also occur in the pelvis, ribs and in other bones. Their prevalence increases with age and at the age of 50 years the remaining lifetime risk of sustaining a fragility fracture has been estimated to be 25% for males and 55% for females.[1] Fragility fractures are associated with increased morbidity, institutionalization, and even mortality.[2] A fracture may lead to substantial (long-term) pain and disability and therefore often negatively impacts the quality of life of patients.[3-5] Hip fractures in particular are associated with a deterioration in health and with mortality. In the typical hip fracture population (mean age of approximately 81 years) it is fatal in 20% to 30% of cases within one year and only 30% will fully recover.[6,7] In the first year following a hip fracture, mortality risk is twice that of the general population of the same age, which is even higher for males (3-4 fold higher risk compared to the general population, depending on age).[8] Emerging evidence now shows that other fracture types are also associated with an increased risk of mortality.[9]

This burden is ever increasing due to the ageing of the population. The annual number of fragility fractures in the European Union has been estimated to be 3.5 million in the year 2010. Together they were responsible for an economic burden of 37 billion euro as calculated from acute health care costs (66% of total costs), long-term health care costs (annual nursing home costs after hip fracture; 28% of total costs), and costs from pharmacological treatment (6% of total costs).[10] By the year 2025, the number of fragility fractures is expected to have increased by 30% to 45%, depending on geographical region.[11] Therefore, key concerns going forward are optimal identification of those at high-risk and optimal implementation of preventive pharmacotherapy among those at high risk.

CLINICAL RISK FACTORS AND BONE FRAGILITY

The epidemiology of fragility fractures reflect influences of bone fragility, environmental and clinical risk factors. (Pharmaco)-epidemiology has contributed greatly to the identification of clinical risk factors. They can be subdivided into patient-characteristics (e.g. increasing age, gender, ethnicity), life-style variables (e.g. smoking, alcohol use, body mass index, mobility), co-morbid conditions (e.g. rheumatoid arthritis, diabetes mellitus, visual impairment), and drug use (e.g. glucocorticoids, psychotropic drugs). The underlying mechanisms that contribute to these associations are multifactorial and complex. For example, after the age of 50 years the incidence of fragility fracture increases to a greater extent among women as compared to men. The increase with advancing age can be explained by both an increase in risk of falling

and bone fragility, which in turn may be either related to co-morbidities, poor mobility, visual impairment or drug-use. The sex difference may be explained by greater bone strength in males, and post-menopausal oestrogen withdrawal in women which causes an accelerated reduction in bone mass and increasing porosity of bone. Another example is the increased fracture risk among individuals with rheumatoid arthritis (RA) which may be explained by an effect on bone due to chronic inflammation with associated cytokine production, inactivity, and an increased risk of falling.[12-16]

Drug-induced fracture risk has been well described for exposure to glucocorticoids and psychotropic drugs, where the latter are frequently used in the general population. Relative risks (RR) for (hip) fracture ranged between 1.3 and 1.9 for current exposure to benzodiazepines,[17] tricyclic antidepressants,[18] SSRIs,[19] anticonvulsants,[20] and antipsychotics[21] as compared to non-use. This may be caused by the underlying disease itself (e.g. depression, epilepsy), an effect on bone or by inducing falls-risk[22] either alone or in combination.

For glucocorticoids bone loss occurs early in the course of use, which is most significant in the first six months.[23,24] Fracture risk also increases rapidly within three to six months of initiating oral glucocorticoid therapy[25] and reverses after discontinuation.[25,26] In addition, there is a dose-response relationship where higher-dosages (> 7.5 mg daily of prednisolone or equivalent) result in significantly higher risks of non-spinal fracture (RR 1.4), hip fracture (RR 2.2) and spinal fracture (RR 2.8) as compared to lower-dosages (< 2.5 mg/day).[27] The mechanisms responsible for glucocorticoid-induced fracture risk relate to an effect on bone by a reduction in bone mineral density (BMD), which is the amount of minerals –such as calcium– in a segment of bone and can be measured by dual-energy X-ray absorptiometry (DXA). The reduction in BMD is mediated by a decrease in bone formation through apoptosis and reduced function of osteoblasts, and to a lesser extent, an increase in bone resorption through enhanced activity of osteoclasts.[24] A meta-analysis of 42,500 individuals, however, suggested that glucocorticoid-induced fracture risk was partially independent of BMD.[28] Indeed, the effect on bone is also mediated by apoptosis of osteocytes which decreases bone micro-architecture and therefore bone quality and strength. In addition, the risk of falling may be increased by muscle weakness or neuropsychiatric symptoms.[24,29]

Reduced BMD is a major risk factor for fracture and has been the cornerstone for diagnosis of the bone disease "osteoporosis". Therefore, a fragility fracture is also termed "osteoporotic fracture" or "major osteoporotic fracture" (hip, spine, forearm, humerus) and this term is used throughout this thesis. Osteoporosis has been operationally defined according to the World Health Organization (WHO) criterion as BMD that lies 2.5 standard deviations or more below the young female adult mean (T-score ≤ -2.5 at lumbar spine or hip)[30] where fracture risk approximately doubles for every standard deviation decrease in BMD. This cut-off value is applied both for men and women and has been implemented as an intervention threshold for pharmacological treatment in guidelines globally.

APPROACHES TO RISK STRATIFICATION

FROM BONE MINERAL DENSITY TO ABSOLUTE FRACTURE RISK

Ideally, patients at high-risk of fracture are identified and subsequently treated in order to prevent a fracture from occurring. In many countries, primary prevention is currently focused on opportunistic case-finding, where referral for BMD testing is triggered by the presence of clinical risk factors. Osteoporotic BMD classifies approximately one quarter of all 70-year old women and approximately half of all 80-year old women as having osteoporosis,[10,30] whereas approximately 50% of women who do sustain a hip fracture do not have osteoporosis by this BMD criterion.[6,31] This proportion is even higher for men and for other fracture types.[31,32] Indeed, it has become evident that BMD does not completely represent other parameters that play a role in bone strength and hence in the risk of fractures, such as bone micro-architecture, bone turnover, and micro cracks. Together with the finding that many clinical risk factors act (partially) independent of BMD on fracture risk,[33] which may be mediated by a higher propensity for falls and reduced bone strength, these insights increasingly lead to the recognition that osteoporotic BMD is a risk factor for fragility fracture rather than a disease in itself and that its sole use is insufficient for the identification of high-risk individuals.

This recognition has led to the development of a considerable number of fracture risk prediction models that incorporate clinical risk factors with or without BMD to predict absolute fracture risk over a specific time frame with the goal to better direct pharmacological treatment to those at high risk.[34] The most comprehensively developed fracture risk prediction model is FRAX which has been developed and launched in the year 2008 by the WHO. It estimates the 10-year risk of hip and major osteoporotic fracture (hip, spine, forearm, or humerus fracture) on the basis of clinical risk factors alone or in combination with BMD (Table 1).[33] The associations between the clinical risk factors and fracture risk were derived from meta-analyses of 9 international prospective community-dwelling cohorts (≈46 000 individuals) and were subsequently validated in 11 independent cohorts (≈230 000 individuals). Importantly, it also incorporates the competing risk of mortality since many risk factors for fracture are also risk factors for mortality. In several countries, FRAX has led to a shift towards absolute risk assessment instead of BMD measurement alone to aid clinical decision making for drug treatment. Indeed, the wide uptake of FRAX is reflected by the number of assessments made on the FRAX web platform (https://www.shef.ac.uk/FRAX), with more than 13 million assessments between 2011 and 2015, and its implementation in an increasing number of clinical guidelines worldwide.[35-39]

TABLE 1 | Risk factors as implemented in the FRAX model for predicting the 10-year risk of hip fracture and major osteoporotic fracture

Risk factor	Definition
Age	40 – 90 years, continuous
Sex	Male or female
Height (m) and weight (kg)	Continuous
Previous fracture	At any site, ever before, yes/no
Parental history of hip fracture	Yes/no
Currently smoking	Yes/no
Alcohol consumption	≥ 3 units per day, yes/no
Secondary osteoporosis	Any of the following; type 1 diabetes mellitus, osteogenesis imperfecta, hyperthyroidism, hypogonadism, premature menopause, malnutrition, malabsorption, chronic liver disease, ever before, yes/no
Rheumatoid arthritis	Ever before, yes/no
Oral glucocorticoids	Current exposure, or exposed for more than 3 months at a dose of prednisolone of 5 mg daily or more (or equivalent doses of other glucocorticoids) ever before, yes/no
Bone mineral density	At the femoral neck (g/cm^2). Alternatively, the T-score based on NHANES III female reference data, optional.

The discrepancy between BMD assessment and absolute fracture risk assessment for clinical decision making can be illustrated by the following examples. Consider a Dutch female aged 53 years, a body mass index of 25 kg/m^2, with no other risk factors but with osteoporotic BMD (T-score -2.5). Despite her diagnosis of osteoporosis, her absolute fracture risk (as calculated by the Dutch FRAX algorithm) is low with a probability of hip fracture and major osteoporotic fracture of respectively 1.4% and 4.2% over the next 10 years. These numbers are respectively 1.9% and 7.3% for a British female with the same characteristics (UK FRAX algorithm), which reflects the geographical differences in fracture risk independent of osteoporotic BMD. The importance of considering clinical risk factors becomes even more clear when a major risk factor for fracture, age, is considered. The same Dutch and British females with osteoporosis, again with a BMI of 25 and no other risk factors but then at the age of 80 years, have considerable higher risks of hip fracture and major osteoporotic fracture despite their shorter life expectancy (Dutch: 5.1%, 12%; British: 6.3%, 17%).

Although FRAX may be an important step forward in the identification of high-risk individuals, major knowledge gaps remain. First, a frequently mentioned limitation of FRAX is that it lacks exposure to psychotropic drugs or a dose-response relationship for exposure to oral glucocorticoids where the latter has been implemented as a dichotomous risk factor only. Psychotropic drugs are frequently used, and not considering exposure to these drugs may underestimate true fracture risk. With regard to glucocorticoids, fracture risk may now be overestimated when patients are exposed to low doses but underestimated with exposure to higher doses.[40]

Second, although FRAX was developed for use in the general community-dwelling population, generalization of predicted fracture risks to subpopulations with known increased fracture risk (e.g. diabetes mellitus type 2,[41] multiple sclerosis,[42] Parkinson's disease,[43] and rheumatoid arthritis [RA][44]) is important. FRAX considers only the presence of rheumatoid arthritis, which is included as a dichotomous risk factor. However, this does not take into account the underlying disease severity where limited evidence has shown higher fracture risk with longer duration of RA disease.[13,44] On the other hand, mortality risk is higher among RA patients as compared to the general population.[45,46] This may result in overestimation of predicted fracture risk, since FRAX adjusts fracture risk for mortality risk by incorporation of population-based mortality rates.[33]

And third, very few external validation studies have evaluated calibration of country-specific FRAX models for risk of hip fracture and major osteoporotic fracture.[34] Yet calibration, which describes the agreement between observed and predicted risks, is a crucial component of a prediction model especially when decision making relies on absolute risk which is the case in several countries with use of FRAX. For major osteoporotic fractures, incidence rates are frequently imputed for calibration of FRAX models by assuming fixed rate ratios between hip and other non-hip fractures as were observed in Sweden over the period 1987-1996, because non-hip fractures often do not require hospitalization and are therefore not routinely registered.[47,48] The validity of this method remains, however, uncertain.

RISK FACTORS FOR FRACTURE AND MORTALITY POST-HIP FRACTURE

A meta-analysis has shown that a history of hip fracture increases the risk of a subsequent fracture by 3.2 times,[49] which is greater than the corresponding risk after a prior fracture at any site (RR 2.1) as is included in FRAX. Few studies, however, have determined which factors pose a patient at increased risk of a future fracture in the high-risk period shortly after the first hip fracture where subsequent fractures cluster in time and risk is especially high in the first year.[50] It is therefore not well understood whether conventional risk factors as in FRAX, e.g. increasing age, are also risk factors for a subsequent fracture after hip fracture. In addition, it is of interest to know whether the 1-year risk of a subsequent fracture has changed over the last decade which may help assist in the understanding of the impact of hip fractures on the health care system where second fractures have an even greater impact on health outcomes including disability and mortality.[9,51] Furthermore, high competing mortality post-hip fracture and any change herein may influence absolute risk of future fracture, where an increase in life-expectancy increases rationale for pharmacological treatment. Indeed, advances in the management of hip fractures (e.g. surgical repair for the more frail patients, faster time to operation, quicker mobilization, reduced length of hospital stay, multidisciplinary rehabilitation services)[52] may have reduced mortality but recent data is scarce. In addition, it remains unknown whether the difference in mortality between hip fracture patients and the general population has changed, which provides a better insight into the change in mortality specifically from hip fracture.

IMPLEMENTATION OF PREVENTIVE PHARMACOTHERAPY IN HIGH-RISK GROUPS

Adequate implementation of effective pharmacotherapy is essential among those at high-risk of fracture. Easily identifiable high-risk groups are those with a prior (hip) fracture and those exposed to (high-dose) glucocorticoids (glucocorticoid-induced osteoporosis; GIOP), where many guidelines instantly indicate anti-osteoporotic drug (AOD) treatment without the consideration of FRAX or BMD assessment. Although patients with these risk factors come under the attention of a physician, a care gap in preventive pharmacotherapy has been described for these patients worldwide.[53] A total of 40% to 90% of GIOP patients did not receive pharmacological treatment,[54-56] and for patients with a prior hip fracture this ranged between 40% and 94% depending on calendar year and country.[57-59] This is despite proven efficacy of pharmacotherapy where bisphosphonates have shown to be effective in increasing BMD and in reducing fracture risk by 30% to 70% in randomised clinical trials in patients with a prior vertebral or hip fracture and / or with osteoporotic BMD.[60] Evidence for anti-fracture efficacy of bisphosphonates in GIOP was primarily extrapolated from its effect on BMD.[61-63] Other effective anti-osteoporosis drugs, including raloxifene, denosumab, teriparatide, and strontium ranelate are also endorsed for fracture risk reduction when bisphosphonates are not indicated because of contra-indications or adverse effects. Inadequate pharmacotherapy can be split up in failure to initiate with treatment, and if initiated; failure to keep taking treatment.

INITIATION WITH ANTI-OSTEOPOROSIS DRUGS FOR SECONDARY FRACTURE PREVENTION

Few studies have determined whether the initiation with anti-osteoporosis drug treatment after hip fracture has changed over the last decade, where clinical guidelines have been developed that address the importance of secondary fracture prevention. And, importantly, prescribing practices were frequently not presented beyond age and gender while other characteristics may influence prescribing practices as well. Individual data linking drug prescribing and patient characteristics (e.g. previous fractures, lifestyle variables, co-morbidities, poly-pharmacy) would greatly assist in determining which patient groups are at increased risk of not receiving AOD treatment after hip fracture and remain at high risk of a future fracture.

INITIATION WITH ANTI-OSTEOPOROSIS DRUGS FOR PREVENTION OF GLUCOCORTICOID-INDUCED OSTEOPOROSIS

In the case of glucocorticoid-induced osteoporosis there is no acute event and physicians may ignore, or are unaware of, the impact of glucocorticoids on fracture risk, which may explain the large proportion of patients that remain untreated. Prior studies that have investigated interventions for improving the prescribing of AODs for glucocorticoid-induced osteoporosis have yielded limited success and involved training of physicians, both general practitioners and rheumatologists, and/or education of patients at risk of glucocorticoid-induced osteoporosis.[64-66]

Pharmacists may play an important role in the implementation of pharmacological prevention of glucocorticoid-induced osteoporosis. They share the responsibility with prescribers to properly inform patients on the advantages and disadvantages of pharmacotherapy and to assist physicians in this respect. In the Netherlands, pharmacists can rapidly, systematically identify all patients who are at risk of glucocorticoid-induced osteoporosis in their computerized order entry systems, because they do not receive AOD treatment. It is therefore of interest to determine whether feedback of the pharmacist to the treating physician may increase the prescribing of AODs in patients eligible for prevention of glucocorticoid-induced osteoporosis.

PERSISTENT USE OF ANTI-OSTEOPOROSIS DRUGS

Data on the anti-fracture efficacy of AODs have been derived from randomised controlled trials with a duration of 3- to 5-years. Prior studies have shown that persistence with therapy (i.e. continued use of treatment over a certain period of time) is an important determinant for the anti-fracture efficacy of AODs in clinical practice.[67,68] It is well known that persistence with AOD treatment is insufficient in real world, as is also observed for treatment of other chronic diseases such as hypertension. Previous studies mostly determined persistence in the first year following instigation of AOD treatment. Subsequently, there is not much known about persistence on the longer term while a duration of use of AOD treatment between 3 to 5 years has been advocated. Furthermore, prior studies did not specifically include patients with a recent fracture and patient-characteristics for non-persistence in this vulnerable group remain poorly documented.[69,70]

THESIS OBJECTIVE

The overall thesis aim was to evaluate and to help improve prediction of absolute fracture risk and the implementation of pharmacological treatment.

More specifically our objectives were:

- To estimate the incidence of hip fracture and major osteoporotic fracture (MOF) in the Netherlands, and to evaluate the imputation method for MOF incidence that was used for calibration of the Dutch FRAX algorithm for the 10-year risk of MOF.
- To validate, and to update if necessary, the UK FRAX algorithm for predicting the 10-year risk of hip fracture and MOF in the general population and in patients affected by rheumatoid arthritis.
- To determine whether addition of a dose-response relationship for exposure to oral glucocorticoids and exposure to psychotropic drugs to conventional FRAX risk factors could increase predictive performance for the 10-year risk of hip fracture.
- To investigate risk factors and changes over time for subsequent fracture and (relative) mortality post-hip fracture.
- To identify the frequency of lack of instigation or non-persistence with anti-osteoporosis drugs for secondary fracture prevention and risk factors for this.

- To determine whether a pharmacy-based intervention could increase the prescribing of anti-osteoporosis drugs in patients eligible for prevention of glucocorticoid-induced osteoporosis.

THESIS OUTLINE

Important features for the prevention of fragility fractures are the identification of individuals at high fracture risk and the implementation of pharmacological treatment which are studied in this thesis. Other preventive measures, such as fall-prevention and lifestyle modifications, therefore remain outside the scope of this thesis.

In **Chapter 2** we focus on the prediction of absolute fracture risk. In **Chapter 2.1** we study the validity of the imputation method that is used for calibration of FRAX for the 10-year risk of major osteoporotic fracture (MOF). In **Chapter 2.2** we externally validate UK FRAX in the general population and in patients affected by rheumatoid arthritis (RA) and test the incremental predictive value of addition of RA disease-specific predictors. Finally, in **Chapter 2.3** we will study whether addition of glucocorticoid dose and psychotropic drugs to conventional FRAX predictors increases predictive performance for the 10-year risk of hip fracture. In **Chapter 3** we study the changes over time in absolute risk of, and risk factors for, subsequent fracture and (relative) mortality post-hip fracture. In **Chapter 4** we focus on the implementation of pharmacological treatment in high-risk individuals, where **Chapter 4.1 and 4.2** are performed among fracture patients, and **Chapter 4.3** among patients at risk of glucocorticoid-induced osteoporosis which incorporates a specific pharmacy-based intervention.

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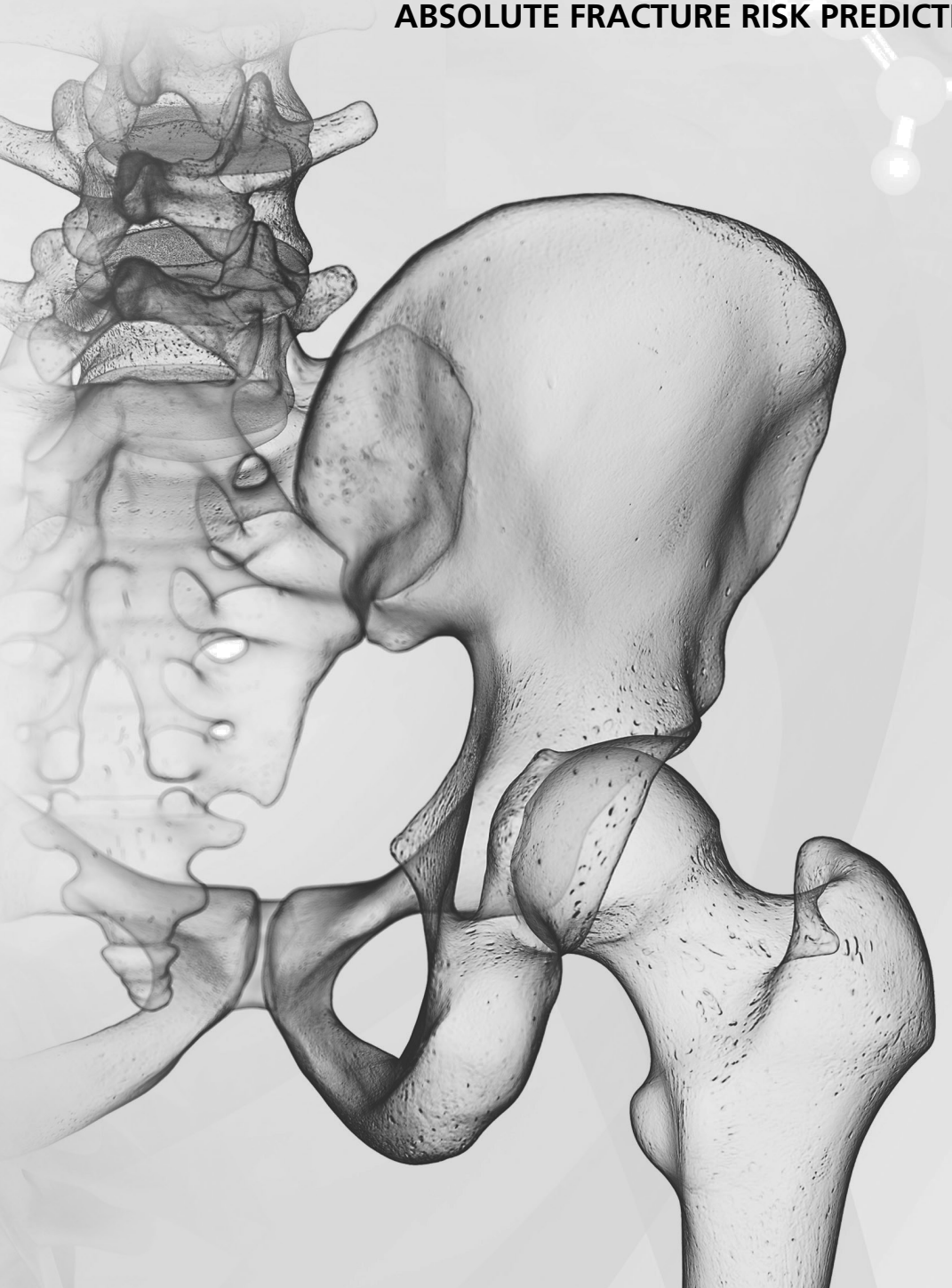
CHAPTER 2

ABSOLUTE FRACTURE RISK PREDICTION



CHAPTER 2.1

The epidemiology of hip and major osteoporotic fractures in a Dutch population of community-dwelling elderly: implications for the Dutch FRAX® algorithm

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ABSTRACT

Background: Incidence rates of non-hip major osteoporotic fractures (MOF) remain poorly characterized in the Netherlands. The Dutch FRAX® algorithm, which predicts 10-year probabilities of hip fracture and MOF (first of hip, humerus, forearm, clinical vertebral), therefore incorporates imputed MOF rates. Swedish incidence rate ratios for hip fracture to MOF (Malmö 1987-1996) were used to perform this imputation. However, equality of these ratios between countries is uncertain and recent evidence is scarce. Aims were to estimate incidence rates of hip fracture and MOF and to compare observed MOF rates to those predicted by the imputation method for the Netherlands.

Methods: Using hospitalisation and general practitioner records from the Dutch PHARMO Database Network (2002-2011) we calculated age-and-sex-specific and age-standardized incidence rates (IRs) of hip and other MOFs (humerus, forearm, clinical vertebral) and as used in FRAX®. Observed MOF rates were compared to those predicted among community-dwelling individuals ≥50 years by the standardized incidence ratio (SIR; 95% CI).

Results: Age-standardized IRs (per 10,000 person-years) of MOF among men and women ≥50 years were 25.9 and 77.0, respectively. These numbers were 9.3 and 24.0 for hip fracture. Among women 55-84 years, observed MOF rates were significantly higher than predicted (SIR ranged between 1.12 – 1.50, depending on age). In men, the imputation method performed reasonable.

Conclusion: Observed MOF incidence was higher than predicted for community-dwelling women over a wide age-range, while it agreed reasonable for men. As miscalibration may influence treatment decisions, there is a need for confirmation of results in another data source. Until then, the Dutch FRAX® output should be interpreted with caution.

INTRODUCTION

Osteoporotic fractures are a worldwide epidemic resulting in significant morbidity, mortality, and high health care costs.[1-3] Due to the ageing population this burden has been projected to increase greatly with an estimated number of 4.5 million fractures in Europe in 2025.[4] It is therefore important to identify those with an increased risk of fracture to direct effective interventions.

The development of the FRAX® algorithm by the World Health Organization has led to a shift in identifying fracture risk from bone mineral density measurement towards absolute risk assessment. This algorithm is intended for primary care and incorporates clinical risk factors with or without bone mineral density (BMD) to compute the 10-year probability of hip or a major osteoporotic fracture ([MOF] first of hip, clinical spine, humerus, or forearm). It has been incorporated internationally in clinical guidelines and is frequently used with over 13 million assessments by the FRAX® webpage between 2011 and 2015.[5-9] Since hip fracture rates do not only vary widely by age and sex but also by geographic region,[2] FRAX® algorithms require country-specific fracture rates and rates for mortality. There are now 62 FRAX® algorithms available for specific countries and ethnicities. The Dutch model has become available in the year 2010.[10]

In contrast to hip fracture, country-specific data for the incidence of MOF are scarce. This is because most fractures at other sites than the hip do not require hospitalization. In the absence of such data, FRAX® algorithms incorporate imputed rates of MOF. This is performed by adopting them from a neighboring country or by assuming equal age-and-sex-specific incidence rate ratios of hip fracture to other MOFs as were observed in Malmö, Sweden.[11] There is, however, only limited evidence that supports the assumption of equal ratios between countries. And importantly, secular changes in incidence of hip and non-hip fractures over the past decade(s) may have violated this imputation method. The Dutch FRAX® algorithm has incorporated hip fracture rates from 2004/2005, and the historical Swedish data (1987-1996) was used to impute MOF incidence. Indeed, a decline in hip fracture incidence was observed in several countries,[2] including Sweden[12] and the Netherlands,[13] but far less is known about fractures at other sites.

We therefore aimed to estimate age-and-sex-specific incidence rates of hip and other MOFs separately (humerus, forearm, clinical spine) and as used in FRAX® (first of hip, humerus, forearm, or clinical spine) in a Dutch community-dwelling population. A second aim was to compare observed MOF rates to those predicted by the imputation method.

METHODS

DATA SOURCE

A cohort study was performed within the Dutch PHARMO Database Network [PHARMO Institute for Drug Outcome Research, www.pharmo.nl]. This network links drug dispensing records to hospital discharge records (www.dutchhospitaldata.nl), general practitioner (GP) and death registration data using probabilistic linkage.[14,15] For the current study these data were available for approximately 660,000 community-dwelling individuals (comprising more than 4.9 million person-years of follow-up) from the Netherlands between 1 January 2002 and 31 December 2011. Primary care diagnoses are coded according to International Classification of Primary Care (ICPC) codes. Hospital records include dates of hospital admission and discharge, diagnoses, procedures and are recorded according to the International Classification of Disease, 9th or 10th revision codes (ICD-9 or ICD-10).[16] High validity of hip fracture coding has been shown previously in the PHARMO record linkage system where >90% of recorded hip fractures represented true hip fractures.[17] The study was approved by the Compliance Committee of the PHARMO Institute. Patient records were anonymized and de-identified by the PHARMO Institute before providing the data to the authors for analysis.

STUDY OUTCOMES

Fractures were classified into the following categories using ICPC, ICD-9 and ICD-10 codes: hip (ICPC: L75.01, ICD-9: 820, ICD-10: S72.0, S72.1, S72.2), forearm (ICPC: L72, ICD-9: 813, 814, ICD-10: S52), clinical spine (ICPC: L76.06, ICD-9: 805, 806, ICD-10: S12.0-S12.2, S12.7, S22.0, S22.1, S32.0-S32.2), humerus (ICPC: L74.04, ICD-9: 812, ICD-10: S42.2-S42.4, S42.7), and the composite category of MOF as defined by the WHO FRAX® algorithm (first of hip, forearm, clinical spine, or humerus). All patients were followed from the index date which was set at one year after start of valid data collection until either the date of right censoring (end date of valid data collection, end of the study period by 31 December 2011, or date of death) or the date of first fracture, whichever came first. The start and end date of valid data collection were respectively the first and last date where data was available in all data sources. This was done separately for each fracture category (hip, forearm, clinical spine, humerus, and the composite category MOF). Patients who sustained a prior fracture within the same category before the index date were excluded from the analyses. When a patient had sustained several fractures within the same category during follow-up, only the first fracture was counted for the calculation of incidence rates.

STATISTICAL ANALYSES

Age-and-sex-specific incidence rates (number of fractures / 10,000 person years) were calculated by dividing the total number of fractures in that specific age-and sex- group by the total number of person years in that group and their 95% Confidence Intervals (95% CIs) were calculated.[18] This was done for 5-year age-categories over the period of valid data collection

from 2002 up to 2011 and was reported from the age of 50 years. Age-standardized fracture rates and their 95% CIs were estimated by the direct method using the age-and-sex-structure of the Dutch population ≥50 years in 2008.[19] Analyses were done separately for each fracture category. Finally, we compared observed age-and-sex-specific MOF rates to those predicted by the standardized incidence ratio (SIR; 95% CI). Predicted MOF rates were calculated by multiplying observed hip fracture rates with equal age-and-sex-specific incidence rate ratios of first hip fracture to first MOF as were observed in Malmö, Sweden which were previously used to calibrate the Dutch FRAX® algorithm for MOF risk.[11, Johansson personal communication] Analyses were performed using SAS statistical software, version 9.2 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

A total of 5373 women aged 50 years and over sustained at least one MOF over 795,133 person-years of follow-up, in contrast to 1959 men over 810,052 person-years of follow-up. Table 1 shows age-and sex-specific incidence rates of first MOF, as well as the incidence of fractures of the hip, forearm, clinical spine, and humerus separately. Fractures of the forearm were the most dominant fracture type in the youngest age categories and hip fractures in the oldest age categories. For women at the age of 50-54 years, 9.6% of MOFs were hip fractures, as compared to 67.5% among those aged 90 years and older. A similar distribution for hip fracture was observed for men. With increasing age, there was a rise in incidence for all fracture categories in both men and women. The lowest incidence of MOF was observed for those 50-54 years (women: 22.2/10,000 person-years, men: 15.0/10,000 person-years) and the highest for those older than 90 years (women: 361.4/10,000 person-years, men: 166.7/10,000 person-years).

Table 2 shows the age-standardized incidence rates for men and women for the composite of MOF as well as for the MOF categories separately. MOF incidence (per 10,000 person-years) in men and women ≥ 50 years of age was estimated at 25.9 (95% CI: 24.7-27.0) and 77.0 (95% CI: 74.9-79.1) respectively. These numbers were 9.3 (95% CI: 8.6-10.0) and 24.0 (95% CI: 22.8-25.2) for hip fracture.

TABLE 1 | Age- and sex-specific incidence rates (per 10,000 person years) of major osteoporotic fractures

	Hip			Forearm			Clinical spine			Humerus			MOF*		
	N	IR	95% CI	N	IR	95% CI	N	IR	95% CI	N	IR	95% CI	N	IR	95% CI
Women															
50-54	35	2.1	1.4-2.8	229	13.9	12.1-15.7	40	2.4	1.7-3.2	65	3.9	3.0-4.9	363	22.2	19.9-24.5
55-59	47	3.0	2.1-3.8	352	22.6	20.2-24.9	57	3.6	2.7-4.6	115	7.3	6.0-8.7	552	35.6	32.6-38.6
60-64	94	6.7	5.4-8.1	417	30.0	27.2-32.9	98	7.0	5.6-8.4	145	10.4	8.7-12.0	717	52.2	48.4-56.0
65-69	103	9.3	7.5-11.1	387	35.3	31.8-38.8	95	8.6	6.8-10.3	144	13.0	10.9-15.1	682	63.2	58.4-67.9
70-74	178	19.3	16.5-22.1	366	40.1	36.0-44.2	129	13.9	11.5-16.3	139	15.0	12.5-17.5	763	85.3	79.3-91.4
75-79	254	35.6	31.2-40.0	337	47.4	42.4-52.5	132	18.3	15.2-21.4	141	19.6	16.4-22.8	795	115.8	107.8-123.9
80-84	330	72.3	64.5-80.1	235	51.0	44.5-57.6	129	27.6	22.8-32.3	117	25.0	20.5-29.6	729	167.4	155.2-179.5
85-89	263	116.5	102.4-130.6	103	44.4	35.8-52.9	80	34.0	26.5-41.4	96	40.9	32.7-49.0	477	223.6	203.5-243.7
90+	199	229.1	197.3-261.0	63	68.1	51.3-84.9	45	48.1	34.1-62.2	27	28.9	18.0-39.7	295	361.4	320.2-402.6
Men															
50-54	36	2.1	1.4-2.7	137	7.8	6.5-9.1	49	2.8	2.0-3.6	42	2.4	1.7-3.1	261	15.0	13.2-16.8
55-59	66	3.8	2.9-4.8	141	8.2	7.0-9.6	67	3.9	3.0-4.8	47	2.7	1.9-3.5	307	18.0	16.0-20.0
60-64	63	4.0	3.0-5.0	136	8.7	7.3-10.2	71	4.6	3.5-5.6	49	3.1	2.3-4.0	305	19.7	17.5-22.0
65-69	51	4.3	3.1-5.5	79	6.7	5.2-8.2	60	5.1	3.8-6.4	35	3.0	2.0-3.9	216	18.5	16.0-20.9
70-74	95	10.6	8.5-12.7	59	6.6	4.9-8.3	68	7.6	5.8-9.4	31	3.5	2.2-4.7	246	27.7	24.3-31.2
75-79	112	18.5	15.1-22.0	47	7.7	5.5-10.0	68	11.2	8.6-13.9	23	3.8	2.2-5.3	240	40.1	35.0-45.2
80-84	121	38.9	32.0-45.8	27	8.6	5.3-11.8	53	16.8	12.3-21.4	13	4.1	1.9-6.4	204	66.4	57.3-75.5
85-89	82	71.7	56.2-87.2	15	12.8	6.3-19.3	26	22.2	13.7-30.8	14	11.9	5.7-18.2	129	114.7	94.9-134.4
90+	37	117.7	79.8-155.6	5	15.4	1.9-28.8	8	24.7	7.6-41.8	5	15.4	1.9-28.8	51	166.7	120.9-212.4

Abbreviations: IR; incidence rate, 95% CI; 95% Confidence Interval, MOF; major osteoporotic fracture
* Includes first fracture of the hip, clinical spine, humerus, or forearm according to the FRAX® definition

TABLE 2 | Incidence rates (per 10,000 person years) of major osteoporotic fractures standardized to the Dutch population

	Men (≥ 50 years)			Women (≥ 50 years)		
Fracture type	No. of fractures	IR	95% CI	No. of fractures	IR	95% CI
MOF *	1959	25.9	24.7-27.0	5373	77.0	74.9-79.1
Hip	663	9.3	8.6-10.0	1503	24.0	22.8-25.2
Forearm	646	8.0	7.4-8.6	2489	31.9	30.7-33.2
Clinical spine	470	6.0	5.5-6.6	805	11.1	10.3-11.8
Humerus	259	3.3	2.9-3.7	989	13.1	12.3-13.9

Abbreviations: IR; incidence rate, 95% CI; 95% Confidence Interval
* Includes first fracture of the hip, clinical spine, humerus, or forearm according to the FRAX® definition

Table 3 shows observed and predicted age-and-sex-specific incidence rates of MOF. Among women, the observed incidence of MOF was significantly higher than predicted over a wide age-range (55 – 84 years). This difference was highest at the age of 65 – 69 years (SIR 1.50; 95% CI: 1.39 – 1.62). In men, the predicted incidence rates agreed reasonably well with those observed, but a significantly higher MOF rate was observed for those 50-54 years (SIR 1.63) and 65-69 years (SIR 1.22). Among the oldest old, the observed MOF rate was lower than predicted which was significant for men 85-89 years (SIR 0.79) and women ≥ 90 years (SIR 0.88).

TABLE 3 | Age-and-sex-specific observed incidence rates of major osteoporotic fracture as compared to those predicted by the imputation method

	$Hip_{observed}$		$MOF_{observed}$		$MOF_{predicted}$ *		
	N	IR	N	IR	N	IR	SIR (95% CI)
Women							
50-54	35	2.1	363	22.2	383	23.4	0.95 (0.85 – 1.05)
55-59	47	3.0	552	35.6	481	31.0	1.15 (1.05 – 1.25)
60-64	94	6.7	717	52.2	507	36.9	1.41 (1.31 – 1.52)
65-69	103	9.3	682	63.2	454	42.1	1.50 (1.39 – 1.62)
70-74	178	19.3	763	85.3	625	69.9	1.22 (1.14 – 1.31)
75-79	254	35.6	795	115.8	586	85.4	1.36 (1.26 – 1.45)
80-84	330	72.3	729	167.4	598	137.3	1.22 (1.13 – 1.31)
85-89	263	116.5	477	223.6	460	215.6	1.04 (0.95 – 1.13)
90+	199	229.1	295	361.4	335	410.1	0.88 (0.78 – 0.99)
Men							
50-54	36	2.1	261	15.0	160	9.2	1.63 (1.44 – 1.84)
55-59	66	3.8	307	18.0	280	16.4	1.10 (0.98 – 1.23)
60-64	63	4.0	305	19.7	338	21.9	0.90 (0.80 – 1.01)
65-69	51	4.3	216	18.5	177	15.1	1.22 (1.06 – 1.39)
70-74	95	10.6	246	27.7	243	27.4	1.01 (0.89 – 1.15)
75-79	112	18.5	240	40.1	230	38.4	1.05 (0.92 – 1.19)
80-84	121	38.9	204	66.4	198	64.6	1.03 (0.89 – 1.18)
85-89	82	71.7	129	114.7	163	144.8	0.79 (0.66 – 0.94)
90+	37	117.7	51	166.7	62	203.6	0.82 (0.61 – 1.08)

Abbreviations: IR; incidence rate, 95% CI; 95% Confidence Interval, MOF; major osteoporotic fracture (first fracture of the hip, clinical spine, humerus, or forearm, according to the FRAX® definition), SIR; standardized incidence ratio.
*Predicted MOF rates were calculated by multiplying observed hip fracture rates by the age-and-sex-specific Swedish incidence rate ratios for first hip fracture to a first MOF. The expected number of MOF fractures were calculated by multiplying the predicted MOF rate to the total number of person-years in the corresponding age-and-sex-specific group.

DISCUSSION

This study provided age-and sex-specific incidence rates of hip and, for the first time**,** MOF as used in FRAX® in a large community-dwelling population in the Netherlands. Forearm fractures were the most dominant fracture type in the youngest age categories and hip fractures in the oldest age categories. The incidence rates of both hip and MOF increased with age for both genders. Among women 55–84 years, the observed incidence of MOF was significantly higher than predicted by the imputation method. In men, the imputation method performed reasonable. Finally, in the oldest old the observed MOF rates were significantly lower than predicted (≥ 90 years in women, and 85-89 years in men).

The general patterns of fracture incidence were in line with previous literature where incidence increased with age, was higher for women, and where forearm fractures were most dominant at younger age and hip fractures at older age.[11, 20-22] However, we found lower age-and-sex-specific incidence rates of vertebral and forearm fractures as compared to those reported by others.[23-26] The Rotterdam Study, a Dutch prospective cohort study, reported approximately 10-fold higher incidence rates of morphometrically ascertained vertebral fractures.[24] Incidence rates of forearm fractures were approximately 2-fold higher.[26] Although only one third[27] to one fourth[28] of all morphometric vertebral fractures come to clinical attention, a 10-fold lower incidence rate indicates substantial under reporting of vertebral fractures in general practitioner records. This finding is supported by a Spanish validation study where under-recording of vertebral and forearm fractures was high in general practitioner records (56% and 50%, respectively) when compared to a prospective cohort study.[29]

Hip fracture rates were also lower when compared to a nationwide study that used hospital discharge records from 2004 to 2005, which was used to calibrate FRAX® to the Dutch population.[10] This may be related to a secular decline in hip fracture incidence that was reported in the Netherlands between 1996 and 2008 with a percentage annual change of -0.64% in women and -0.34% in men.[13] This study used nationwide data that was corrected for missing values by Statistics Netherlands. From the year 2005, Dutch hospitals were no longer required to record hospitalisations by ICD-codes and send them to the national registry. This has led to an increase in missing or non-linking records from 3.5% in 2002 to 14% in 2007.[10,30] Imputation resulted in missing's ranging between 2.6% and 3.5% due to non-linking records over the same period. To overcome this limitation, we linked hospitalisations to general practitioner records but under recording may still have been present. A further explanation may be a difference in general health between the study population and the total population of the Netherlands. The present study only included community-dwelling individuals while the incidence of hip fracture has been reported to be 2 to 20-fold higher in institutionalized patients, depending on age and sex.[31,32] Indeed, the Global Longitudinal Study of Osteoporosis in Women (GLOW, 2006-2013) that prospectively estimated hip

fracture incidence in an international population-based community-dwelling population, found similar hip fracture rates (80-84 years: 70.0/10,000 person-years).[22,33]

The higher observed incidence of MOF as compared to that predicted by the imputation method is in line with scarcely available evidence from other countries.[22,34,35] A Canadian study used hospitalisation and claims data to obtain the hip fracture/MOF incidence rate ratios over the period 2000–2007.[34] The Canadian ratios were significantly higher than the Swedish ratios for women 55–74 years while this was only observed among men 55–59 years. An Icelandic study showed a significantly higher MOF incidence as compared to that predicted among women 60–69 years (33%) and among men 50–59 years (28%).[35] Furthermore, although the total number of fractures was limited, the GLOW study similarly reported higher hip/MOF ratios than those reported in Sweden.[22]

Any miscalibration of FRAX® will influence predicted absolute fracture risk, and subsequently the individual risk communication between the physician and the patient and the decision to prescribe anti-osteoporotic drugs. It may have a substantial impact on treatment decisions worldwide, since the online FRAX® tool is frequently used with over 13 million hits between 2011 and 2015 where the majority of the country-specific FRAX® tools incorporate imputed MOF rates due to lack of data. Specific treatment thresholds for FRAX® are not incorporated into Dutch guidelines, but several international guidelines (e.g. the USA) specifically state to initiate treatment above a certain threshold of FRAX® predicted absolute fracture risk. Indeed, a simulation study showed that a 20% underestimation in MOF risk resulted in a 50% decrease in the numbers categorized as needing treatment when the treatment threshold was set at 20%.[36]

Apart from differences in geographic region, a possible explanation for the underestimation of MOF incidence by the imputation method is a secular change in fracture incidence, where the drop in MOF incidence proceeded more slowly than for hip fracture alone. The decline in hip fracture incidence in the Netherlands was greatest among the younger age categories (65-69: -23%, 70-79: -13.9%, 80-84: -5.4%) and among women.[13] Over the same time period, forearm fracture incidence declined, but less marked than at the hip, among younger women (60-69; -18.4%, 70-79; -5%) while rates remained stable among the elderly.[37] Vertebral fracture incidence has even increased in both Dutch men and women aged ≥ 65 years.[23] The slower decline in incidence of MOF as compared to the hip was similarly observed in the limited number of studies that evaluated secular trends for hip and non-hip major osteoporotic fractures, including Canada[21] and Iceland.[20]

The reasons for the secular changes in fracture epidemiology remain poorly understood. It may be related to increased health and functional ability of the population.[38,39] A change in frequency of risk factors for fracture such as physical activity, vitamin D insufficiency, and

smoking status may all have contributed to changes in fracture risk. The increase in body mass index, which was reported worldwide,[40] may also have reduced hip fracture risk. The implementation of anti-osteoporosis drug treatment or fall prevention programs could further have contributed to reduced fracture risk, but is unlikely to be fully responsible since the secular decline in hip fracture incidence initiated already before these measures. Furthermore, one should consider data quality when interpreting secular changes in fracture incidence. This includes knowledge of changes in the coding system, and of increases[41] or decreases in the rate of reporting. Finally, incidence rates may be influenced by the underlying study population which in turn is influenced by the way databases are being linked. For example, linkage of a community pharmacy-based cohort to hospitalisations, as used in this study, excluded the institutionalized population.

The Dutch FRAX® algorithm was calibrated with higher hip fracture rates than observed in the present study.[10] The imputed MOF rates are therefore still equivalent or higher than the MOF rates from the present study, despite evidence for violation of the Swedish hip to MOF imputation method. We could not reliably calculate true age-and-sex-specific hip/MOF ratios as non-hip MOFs were likely under-recorded in our database. It is important to use other data sources to update the fracture epidemiology in the Netherlands and to confirm our results. An alternative for estimating fracture incidence is claims data. The Dutch VEKTIS database has nationwide coverage with complete fracture data. However, patient-specific data should be available since aggregated age-and-sex-specific data leads to inability to adjust incidence for previous or subsequent fractures. This would result in substantially higher IRs and thus overestimation of MOF risk when these rates were used to calibrate FRAX®, as was observed in an Icelandic study.[35] A further drawback includes the lag time of up to two years in registration of claims data. A second alternative may be linkage of general practitioner records to emergency department records where all non-hip fractures enter the system. Linkage to GP records then would enable calculation of incidence rates on a patient-level.

Our study had additional limitations. Due to the probabilistic linkage process we may have missed fractures. In addition, the source population was not fully representative of the total population and results can therefore not be extrapolated to the institutionalized population. Third, fractures were ascertained from administrative data which is less reliable than radiographic or medical chart review. However, a high positive predictive value (>90%) has been shown for hip, vertebral, and forearm fractures in general practitioner records[29,42] and for hip fracture in the PHARMO Database Network.[17] Finally, a more general limitation of FRAX® includes that many other fracture sites than those included in FRAX® have been associated with osteoporosis.[22,43] Their neglect may underestimate true fracture risk.

A major strength of this study included the linkage of longitudinal general practitioner, hospitalization and mortality records for a reasonably large part of the Netherlands. It allowed

anonymized person-specific follow-up to estimate the incidence of MOF as used in FRAX®. The Rotterdam Study[24,26] also estimated fracture incidence at a patient-level, but not for MOF as used in FRAX® and extrapolation of results may have been hampered as this study was performed in the region of Rotterdam only.

In conclusion, observed MOF incidence was higher than predicted by the imputation method for women over a wide age range while there was reasonable agreement among men. Despite evidence for invalidity of the imputation method to estimate MOF incidence, the Dutch FRAX® algorithm currently incorporates equivalent or higher incidence rates for MOF due to higher hip fracture rates. As miscalibration may affect treatment decisions, there is a need for confirmation of results in another data-source. Until then, the Dutch FRAX® output should be interpreted with caution.

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CHAPTER 2.2

Predicting the 10-year risk of hip and major osteoporotic fracture in rheumatoid arthritis and in the general population: an independent validation and update of UK FRAX without bone mineral density

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ABSTRACT

Objectives: FRAX incorporates rheumatoid arthritis (RA) as a dichotomous predictor for predicting the 10-year risk of hip and major osteoporotic fracture (MOF). However, fracture risk may deviate with disease severity, duration, or treatment. Aims were to validate, and if needed to update, UK FRAX for RA patients and to compare predictive performance with the general population (GP).

Methods: Cohort study within UK Clinical Practice Research Datalink (CPRD) (RA: n=11 582, GP: n=38 755), also linked to hospital admissions for hip fracture (CPRD-Hospital Episode Statistics, HES) (RA: n=7221, GP: n=24 227). Predictive performance of UK FRAX without bone mineral density (BMD) was assessed by discrimination and calibration. Updating methods included recalibration and extension. Differences in predictive performance were assessed by the C-statistic and Net Reclassification Improvement (NRI) using UK National Osteoporosis Guideline Group intervention thresholds.

Results: UK FRAX significantly overestimated fracture risk in patients with RA, both for MOF (mean predicted vs. observed 10-year risk: 13.3% vs 8.4%) and hip fracture (CPRD: 5.5% vs 3.1%, CPRD-HES: 5.5% vs 4.1%). Calibration was good for hip fracture in the GP (CPRD-HES: 2.7% vs 2.4%). Discrimination was good for hip fracture (RA: 0.78, GP: 0.83) and moderate for MOF (RA: 0.69, GP: 0.71). Extension of the recalibrated UK FRAX using CPRD-HES with duration of RA disease, glucocorticoids (>7.5 mg/day) and secondary osteoporosis did not improve the NRI (0.01, 95% CI -0.04 to 0.05) or C-statistic (0.78).

Conclusions: UK FRAX overestimated fracture risk in RA, but performed well for hip fracture in the GP after linkage to hospitalisations. Extension of the recalibrated UK FRAX did not improve predictive performance.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disease characterised by destruction of periarticular bone and joint structures and has been associated with osteoporosis.[1,2] The risk of hip fracture,[3-5] morphometric or clinical spine fracture[2,6] and of other fractures is increased.[3,5] The underlying reasons for the increased fracture risk in RA are complex. They may include chronic inflammation, inactivity and an increased risk of falling.[1,7] RA has therefore been incorporated as a dichotomous predictor in the WHO FRAX algorithm for predicting the 10-year risk of hip or major osteoporotic fracture (MOF; hip, clinical spine, forearm, humerus).[8]

There is, however, uncertainty about the predictive performance of FRAX in RA.[9] FRAX may underestimate fracture risk in patients with more severe RA, since it does not take the underlying disease activity and resulting joint damage into account. Conflicting results have been reported for correlation of the Health Assessment Questionnaire with clinical fracture risk, which is an often used measure for functional ability in RA,[10-12] and limited evidence has shown higher fracture risk with longer duration of disease.[3,13] On the other hand, FRAX may overestimate fracture risk due to higher mortality among patients with RA as compared with the general population, [3,14] since FRAX adjusts fracture risk for competing mortality risk. Furthermore, the role of glucocorticoids on fracture risk in RA is uncertain where fracture risk was found to be independent of glucocorticoid use,[3] but preservation of bone mineral density (BMD) has also been described with use of low-dose oral glucocorticoids (GCs).[15-18]

Therefore, this study aimed to validate UK FRAX for the 10-year risk of hip or MOF in patients with RA and to compare predictive performance with the general population. If needed, methods to recalibrate or extend UK FRAX were applied to improve its predictive performance.

METHODS

SOURCE POPULATION

A cohort study was conducted within the Clinical Practice Research Datalink (CPRD) (http://www.cprd.com). This database contains computerised medical records of 625 primary care practices in the UK, representing 8% of the total population. Data recorded in CPRD includes demographic information, laboratory tests, primary care diagnoses, specialist referrals, hospital admissions, prescription details and lifestyle variables such as body mass index (BMI), smoking status and alcohol consumption. Previous studies have shown high validity of hip fracture registration (>90% was confirmed),[19] and high degrees of accuracy and completeness of data have been shown for other diagnoses and mortality.[20-23] Linkage of CPRD data to Hospital Episode Statistics (CPRD-HES) was eligible for 62% of the population captured within CPRD, all residing in England. Linkage to HES provides all hospital admissions including the date of discharge and the cause. Approval for this study was given by the

Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare products Regulatory Agency (MHRA) Database Research (protocol number 15_023A).

STUDY POPULATION

Data between 1 January 1987 and 31 December 2013 were extracted from CPRD. HES diagnoses were available between 1 April 1997 and 31 December 2013. We selected all patients with RA at 1 January 2004 (index date), who also had ≥1 year of data collection before the index date. We chose 1 January 2004 as the index date to allow for follow-up of 10-years. RA was defined by a previously validated algorithm[24]; ≥ 1 disease-modifying anti-rheumatic drug (DMARD) prescription after first RA diagnosis code. In line with FRAX, all patients had to be between 40 and 90 years at the index date and were excluded when they were exposed to any anti-osteoporosis drug (AOD; bisphosphonates, raloxifene, strontium ranelate, denosumab, parathyroid hormone) ever before the index date.

We matched up to four controls from the general population to every patient with RA by age, sex and practice in order to directly compare the predictive performance of FRAX between the RA cohort and the general population.

OUTCOMES

The occurrence of hip fracture and the composite of MOF (first of hip, forearm, clinical spine, humerus) were ascertained by medical codes in CPRD. Hip fractures were measured in CPRD-HES by International Classification of Diseases and Related Health problems (ICD-10) codes S72.0, S72.1, S72.2.

DEFINITION OF PREDICTORS

In records before the index date, FRAX predictors were determined; age at index date, sex, BMI (most recent), previous fracture at any site (ever before, yes/no), current smoking status (most recent; yes/no), alcohol use (most recent medical code for alcohol abuse or for alcohol use where the daily number of units was ≥3, yes/no), oral glucocorticoid use (prescription within 90 days before or ≥ two prescriptions with a mean daily dose of prednisolone [equivalents] of ≥ 5 mg in the year before, yes/no), RA (ever before[24], yes/no) and secondary osteoporosis (ever before, medical code for type 1 diabetes mellitus, osteogenesis imperfecta, hypogonadism, premature menopause, malnutrition or malabsorption or chronic liver disease, yes/no). A parental history of hip fracture was not available. Therefore, we calculated a weighted average of the risks when assuming a parental hip fracture and by assuming absence of parental hip fracture based on a prevalence of parental hip fracture of 12%.[8] An RA specific predictor, duration of RA disease, was defined as years between the date of RA diagnosis and the index date.[3] Rheumatoid factor-positive RA was not included because of unrealistically low prevalence (1.9%). Finally, oral glucocorticoid use was alternatively defined by mean daily dose in the year before (< 2.5, 2.5 – 7.5 and > 7.5 mg/day).

Missing values for BMI, smoking status and alcohol use were imputed by multiple imputation using all predictors and the outcome variable, resulting in five imputed datasets. Analysis by multiple imputation gives unbiased results under the less restrictive missing at random assumption instead of missing completely at random, and generally less bias than complete case analysis if data are missing not at random.

STATISTICAL ANALYSES

Predicted 10-year risks of hip fracture and MOF were calculated by UK FRAX (FRAX desktop V3.9) without information on BMD for every patient. This was repeated for each imputed dataset to provide the mean predicted risks (95% CI). The observed 10-year risk of hip fracture and MOF was estimated by the cumulative incidence function (%) to comply with the outcome definition of FRAX, where fracture risk is adjusted for mortality risk (i.e. sustaining a fracture within remaining lifetime up to 10 years), and to account for loss-to-follow up.[25] Fractures were measured between index date and death, end of the study period (truncated at 10 years following index date, 31 December 2013) or moving out of CPRD, whichever came first. Predictive performance was assessed by measures of discrimination (C-statistic) and calibration (on average and by percentiles of predicted risk). In a sensitivity analysis, observed risks among those using AODs after index date were increased inversely proportional to the estimated effect of AODs on hip fracture (assuming a relative risk of 0.5[26]) to determine the influence of AOD use on the average observed risk.

Recalibration was performed for hip fracture in CPRD-HES by fitting the log-odds transformed FRAX probabilities (ie, the linear predictor) as a single continuous covariate in a logistic regression model with hospitalisation for hip fracture within 10 years as the outcome variable (CPRD-HES provided full coverage for hip fracture).[27,28] Thereafter, individual FRAX predictors were added to the linear predictor to determine whether these had an additional predictive effect, and also glucocorticoid dose and duration of RA disease were included. Interactions between the linear predictor and FRAX predictors, glucocorticoid dose and duration of RA disease were also tested. The final (updated) model was derived by including all variables and interactions that were significantly related to hip fracture risk in a multivariable model and then performing backward elimination. In a sensitivity analysis, AOD treatment after the index date and its interaction terms were included into the model.

We determined whether hip fracture prediction was improved for the extended model compared with the recalibrated UK FRAX model in terms of discrimination (C-statistic) and category-based Net Reclassification Improvement (NRI).[29,30] The NRI incorporates age-specific intervention thresholds set by the National Osteoporosis Guideline Group, which are linked to FRAX output in the UK. Positive NRI values indicate adequate reclassification of risk, whereas negative values indicate inadequate reclassification of risk. Bootstrapping (500 repetitions) was performed to correct the C-statistic for optimism.[31] A shrinkage factor was applied to the

β-coefficients of the final models. All statistical analyses were performed using SAS V9.4 (SAS, Cary, North Carolina, USA). A p value < 0.05 was considered statistically significant.

RESULTS

A total of 16 331 patients with RA were identified, of which 1031 were excluded because they were aged < 40 or > 90 years, and 3718 because they were previously exposed to an AOD. This left 11 582 patients with RA for analyses with 297 and 808 incident cases of hip fracture and MOF and 2733 deaths in CPRD, respectively. HES linkage reduced the number of patients with RA to 7221 (247 hip fractures, 1699 deaths). Table 1 details the characteristics of the RA population in CPRD and in CPRD-HES. The matched cohort from the general population comprised of 38 755 individuals with 536 and 1925 incident cases of hip fracture and MOF, and 5636 deaths in CPRD, respectively. HES linkage reduced the number to 24 227 (476 hip fractures, 3550 deaths).

TABLE 1 | Characteristics of the RA study population in CPRD and in CPRD – HES

Characteristic	CPRD (n=11 582)	CPRD – HES (n=7221)
Median follow-up, years (IQR)	9.0 (4.7 – 10)	9.0 (5.3 – 10)
Sex, n (%)		
Male	3729 (32.2)	2263 (31.3)
Female	7853 (67.8)	4958 (68.7)
Age, years, mean (± SD)	62.9 (11.4)	63.0 (11.5)
Body mass index, kg/m^2, mean (± SD)	26.8 (5.3)	26.7 (5.3)
Missing	1780 (15.4)	1086 (15.0)
Current smoking, n (%)	4147 (35.8)	2573 (35.6)
Missing, n (%)	890 (7.7)	547 (7.6)
Alcohol use ≥ 3 units per day, n (%)	580 (5.0)	371 (5.1)
Missing, n (%)	1759 (15.2)	1081 (15.0)
Previous fracture, n (%)	1908 (16.5)	1184 (16.4)
Glucocorticoid use yes/no*, n (%)	1806 (15.6)	1176 (16.3)
Glucocorticoid use, daily dose**, mean (± SD)	4.9 (3.2)	4.9 (3.2)
0 < GC < 2.5 mg/day, n (%)	508 (4.4)	295 (4.1)
2.5 ≤ GC ≤ 7.5 mg/day, n (%)	1160 (10.0)	786 (10.9)
> 7.5 mg/day, n (%)	305 (2.6)	200 (2.8)
Secondary osteoporosis, n (%)	580 (5.0)	372 (5.2)
Age of RA onset, years, mean (± SD)	52.8 (13.5)	52.8 (13.7)
RA disease duration, years, mean (± SD)	10.1 (9.2)	10.2 (9.3)
< 2 years since diagnosis	1336 (11.5)	824 (11.4)
2 – 10 years since diagnosis	5900 (50.9)	3671 (50.8)
>10 years since diagnosis	4346 (37.5)	2726 (37.8)

Abbreviations: CPRD, Clinical Practice Research Datalink; GC, oral glucocorticoids; HES, Hospital Episode Statistics; RA, Rheumatoid Arthritis; IQR, interquartile range; SD, standard deviation
*Glucocorticoid use was defined as in FRAX: prescription within 90 days before or ≥ two prescriptions with a mean daily dose of prednisolone (or equivalents) of ≥ 5 mg in the year before.
** Glucocorticoid use was defined as ≥ two prescriptions with a mean daily dose of prednisolone (or equivalents) of < 2.5 mg/day, 2.5 – 7.5 mg/day or > 7.5 mg/day in the year before

UK FRAX overestimated fracture risk among the RA population in CPRD, both for MOF (mean predicted vs observed 10-year risk: 13.3% vs 8.4%, 95% CI 7.8 to 9.0) and for hip fracture (5.5% vs 3.1%, 95% CI 2.8 to 3.5) (Figure 1). Linkage to hospitalisation data for hip fracture attenuated the overestimation, but it remained significant (5.5% vs 4.1%, 95% CI 3.6 to 4.6) (Figure 2a). The AOD-adjusted mean observed risk was 4.6% (25% received an AOD). C-statistics were 0.78 and 0.69 for hip fracture and MOF, respectively.

In the general population, UK FRAX also overestimated the risk of MOF (8.6% vs 6.2%, 95% CI 5.9 to 6.4) and hip fracture in CPRD (2.7% vs 1.8%, 95% CI 1.6 to 1.9). After linkage to hospitalisations, there was close agreement between predicted and observed risks of hip fracture (2.7% vs 2.4%, 95% CI 2.2 to 2.7) (Figure 2b). The AOD-adjusted mean observed risk was 2.5% (6% received an AOD). C-statistics were 0.83 and 0.71 for hip fracture and MOF, respectively.

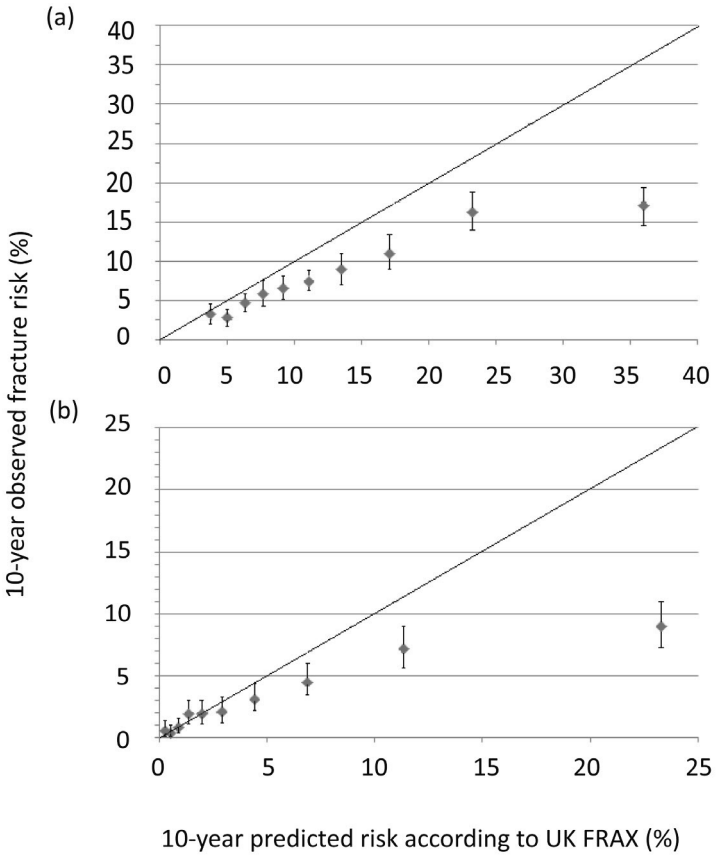

FIGURE 1 | Calibration plot for prediction of (a) major osteoporotic fracture and (b) hip fracture by UK FRAX (Clinical Practice Research Datalink) among patients with rheumatoid arthritis, by percentiles of predicted risk

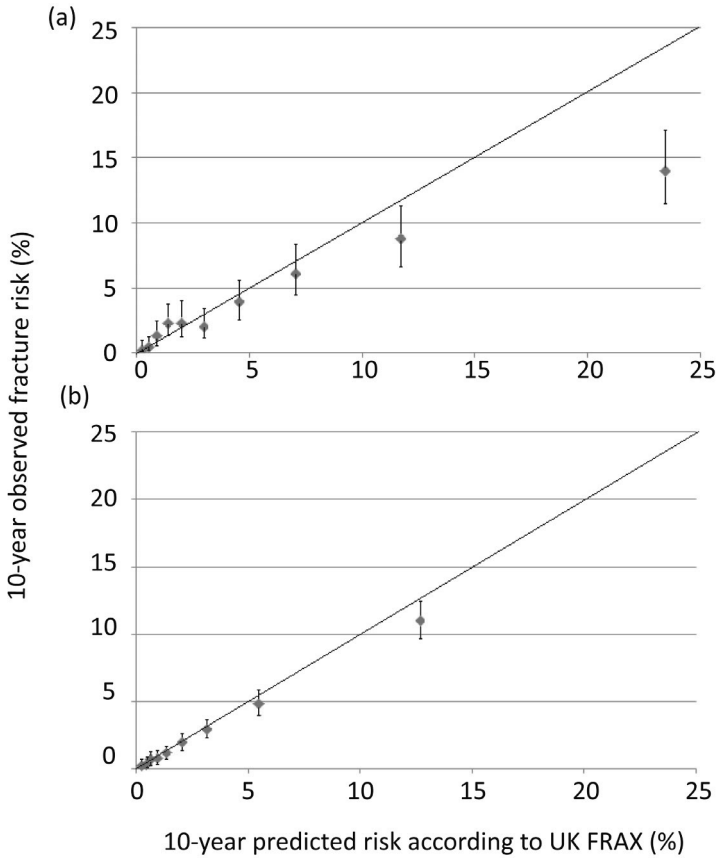

FIGURE 2 | Calibration plot for prediction of hip fracture by UK FRAX (Clinical Practice Research Datalink-Hospital Episode Statistics) among (a) patients with rheumatoid arthritis and (b) the general population, by percentiles of predicted risk

The higher observed risk of hip fracture in CPRD-HES as compared to CPRD indicates underascertainment of hip fractures in CPRD. Updating of UK FRAX was therefore not performed for MOF, but only for hip fracture in CPRD-HES for patients with RA. The recalibrated UK FRAX model for hip fracture in RA is shown in Table 2. The extended model included the linear predictor, duration of RA disease and its interaction with the linear predictor, high-dose glucocorticoids (> 7.5 mg/day) and secondary osteoporosis (Table 2). In sensitivity analyses, AOD treatment and its interaction with the linear predictor were dropped from the recalibrated model (adjusted (adj.) OR for AOD treatment: 0.6, 95% CI 0.3 to 1.1, adj. OR for interaction: 0.8, 95% CI 0.7 to 1.1) and the extended model (adj. ORs of 0.6, 95% CI 0.3 to 1.1 and 0.8, 95% CI 0.7 to 1.1), respectively, during backward elimination.

TABLE 2 | Recalibrated and extended UK FRAX for 10-year risk of hip fracture (CPRD – HES) in RA

	β-coefficient	OR (95% CI)	Shrunken β-coefficient**
Recalibrated UK FRAX			
Intercept	-1.085	-	-1.080
UK FRAX *	0.757	2.13 (1.92 to 2.37)	0.749
Extended UK FRAX			
Intercept	-0.728	-	-0.713
UK FRAX *	0.939	2.56 (2.17 to 3.02)	0.921
Secondary osteoporosis (yes/no)	0.521	1.68 (1.04 to 2.74)	0.511
Glucocorticoid > 7.5 mg/day (yes/no)	-1.303	0.27 (0.09 to 0.87)	-1.276
Duration of RA disease (per year increase)	-0.029	0.97 (0.95 to 0.99)	-0.029
Duration of RA disease * UK FRAX *	-0.015	0.99 (0.98 to 0.99)	-0.015

Abbreviations: OR, odds ratio; 95% CI, 95% Confidence Interval; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; RA, rheumatoid arthritis
* Log odds transformed 10-year risks of hip fracture ($\ln(prob_{hip} / (1\text{-}prob_{hip}))$) as derived from the original UK FRAX algorithm
** The shrunken β-coefficients were derived by applying the shrinkage factor (0.98 for the extended model and 0.99 for the recalibrated model) to the original β-coefficients.

Calibration of the extended model was good (intercept: 0.00, β linear predictor: 1.02) (Figure 3). The C-statistic was 0.78. Extension did not improve correct classification of hip fracture cases and non-cases when compared with the recalibrated UK FRAX model with an NRI of 0.01 (95% CI -0.04 to 0.05) (Table 3).

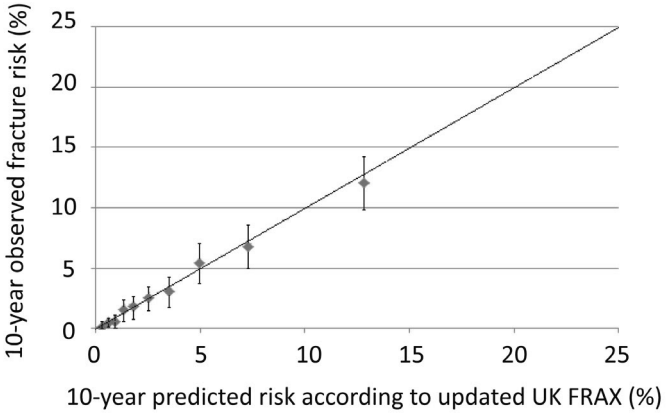

FIGURE 3 | Calibration plot for prediction of hip fracture by the updated UK FRAX (Clinical Practice Research Datalink-Hospital Episode Statistics) among patients with rheumatoid arthritis, by percentiles of predicted risk

TABLE 3 | Reclassification of hip fracture cases and non-cases with RA (CPRD-HES) with addition of duration of RA disease, high-dose glucocorticoids and secondary osteoporosis to the recalibrated UK FRAX model, using age-specific NOGG intervention thresholds*

	Extended UK FRAX			
Recalibrated UK FRAX	Above threshold	No change	Below threshold	Total
Total, n	407	6508	306	7221
Hip fracture cases, n	18	216	13	247
Hip fracture non-cases, n	389	6292	293	6974

Abbreviations: BMI, body mass index; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; NOGG, National Osteoporosis Guideline Group; RA, rheumatoid arthritis
***** The intervention threshold is set at the probability of hip fracture equal to that of a woman, with BMI 24 kg/m^2, and prior fracture, for a specific year of age and is applied to both men and women.

DISCUSSION

UK FRAX overestimated the risk of hip fracture and MOF in CPRD for both the RA population and the general population. Linkage to hip fracture hospitalisations changed this finding, where calibration was good for the general population but overestimation of UK FRAX for hip fracture remained among patients with RA. Discrimination was good for hip fracture and moderate for MOF in both populations. Extension of the recalibrated UK FRAX model for RA with duration of RA disease, high-dose glucocorticoids, and secondary osteoporosis did not improve predictive performance.

Little is known about fracture risk assessment in RA[32,33] and we are not aware of studies that have determined discrimination and calibration of FRAX, which has been developed and validated in the general population, in this subpopulation. Lee *et al.*[33] applied the Korean FRAX algorithm to 545 Korean patients with RA, and found no difference in fracture incidence between those who met the FRAX thresholds for treatment and those who had osteoporosis. However, the Korean FRAX model was not validated, which limits the interpretation of results. In order to determine whether external influences other than RA itself influenced the performance of FRAX, we have also evaluated FRAX in a random sample from the general population. Worldwide, a limited number of independent external validation studies have been performed for FRAX and even fewer have assessed calibration.[34] To date, one study has evaluated calibration of FRAX in the general population of the UK.[35] This study was performed in the QResearch primary care database, where UK FRAX overestimated hip fracture risk in each percentile of predicted risk. This finding was likely the result of underascertainment of (hip) fractures in primary care data. Indeed, we found calibration to be improved upon linkage of CPRD to HES data. It remains, however, unclear how well UK FRAX calibrates for MOF risk. The higher discrimination of FRAX for hip fracture as compared with MOF is well in line with findings from other external validation studies.[34] This may be the result of a different association of risk factors for different fracture types.[35]

A possible explanation for the overestimation of hip fracture risk by FRAX in RA is higher competing mortality as compared with the general population.[14,36] Their lifespan is reduced by 3-10 years, for which no improvement has been found over the past decades.[14,36] Also, all patients with RA were exposed to DMARDs. These drugs have been associated with a protective effect on loss of BMD and reduced fracture risk, but evidence has been conflicting.[9,37] Biologics are now frequently used among patients with RA and may further reduce fracture risk, although the adjusted risk of non-vertebral fracture has been reported to be similar across patients with RA starting a tumour necrosis factor-α inhibitor, methotrexate or other non-biologic DMARDs.[37] In addition, AOD treatment may have influenced observed fracture risks, but our results suggest that the overestimation of FRAX was (largely) independent of AOD treatment status. The adjusted observed risk for hip fracture remained lower than predicted when we assumed a 50% relative risk reduction among all patients treated with AOD. Similarly, a Canadian prospective cohort study found that AOD treatment status did not appear to interfere with the predictive performance of the Canadian FRAX algorithm in the general population.[38] Treatment duration influenced this finding for hip fracture but not for MOF, where observed risks were significantly lower than predicted among patients adhering to AOD treatment for at least 5 years. The insufficient adherence to AOD treatment in clinical practice is well known, which has been shown to blunt the antifracture effectiveness, and may explain the independence of FRAX calibration from AOD treatment status.[39]

The finding that overestimation of UK FRAX for risk of hip fracture increased with longer duration of RA may relate to increased competing mortality with longer duration of RA disease,[36] and greater loss of BMD during recent onset of disease. Second, patients with RA who were exposed to high-dose glucocorticoids had a lower risk of hip fracture, which was independent from the risk of hip fracture with use of glucocorticoids as defined in FRAX. The role of glucocorticoids on fracture risk in RA is not well understood. Inconsistent results were reported for the association between bone loss and exposure to low-dose to medium-dose glucocorticoids.[15-18,40] Our finding may be related to increased mortality among those who are treated with high-dose GCs.[41,42] The present study, however, was not designed to determine the causal association between glucocorticoid dose and hip fracture risk in RA. And third, secondary osteoporosis was selected as a predictor for the 10-year risk of hip fracture on top of FRAX. FRAX neglects the influence of secondary osteoporosis when RA is present, but our finding is not in line with this assumption. Most importantly, however, is that our results show that their addition to the recalibrated UK FRAX did not improve identification of RA individuals at high risk of hip fracture.

This study has several strengths. The included patients with RA were representative for the general RA population with a similar age at onset of RA disease and gender distribution as was previously reported.[43,44] In addition, this is the first study that provides results for calibration of UK FRAX for RA and also for the general population, where hip fractures were

completely captured and which enabled 10 years of follow-up. A limitation was that we had no data on BMD and RA disease severity parameters besides duration of RA disease.[9] When access to dual energy X-ray absorptiometry is limited,[45,46] however, FRAX without BMD may be used instead and a strong correlation between fracture risks by FRAX without and with BMD has been shown.[47] Furthermore, information on parental hip fracture was not available. Therefore, we have calculated weighted average risks by assuming the prevalence of parental hip fracture as was observed in the FRAX developmental cohorts. This was done not to influence the average calibration and to evaluate methods to improve this, and this method resulted in good calibration of FRAX for hip fracture in the general population. We were also not able to determine whether duration of RA disease interacted with the individual predictors since β-coefficients of the original FRAX algorithm are not publicly available.

In conclusion, UK FRAX overestimated hip fracture and MOF risk in RA and in the general population when fractures were measured in primary care data. Linkage to hospitalisations for hip fracture showed good calibration for the general population, but overestimation remained in the RA population. Discrimination was good for hip fracture and moderate for MOF in both populations. Updating of UK FRAX for RA beyond recalibration did not improve predictive performance for hip fracture.

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CHAPTER 2.3

Incremental predictive value of extending FRAX predictors with glucocorticoid dose and psychotropic drugs for the 10-year risk of hip fracture

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Submitted for publication

ABSTRACT

Introduction: Identifying individuals who are at an increased risk of hip fracture is important, since hip fractures are associated with high morbidity, mortality and a major economic burden. The most utilized prediction tool, FRAX, has been criticized for not including psychotropic drugs or a dose-response relationship for glucocorticoids. This study therefore aimed to determine whether addition of these predictors to FRAX predictors could increase predictive performance for hip fracture.

Methods: Population-based cohort study within the UK CPRD (n=312 331) and linked to hospital admissions for hip fracture (CPRD-HES) (n=193 516). Prediction models for the 10-year risk of hip fracture were derived by Fine and Gray regression analysis. A base model with FRAX predictors and an extended model with FRAX predictors, psychotropic drug classes and glucocorticoid dose were developed. Calibration was assessed by percentiles of predicted risk. Differences in predictive performance were assessed by the C-statistic and Net Reclassification Improvement (NRI) using age-specific UK NOGG intervention thresholds.

Results: Hip fracture incidence was significantly lower in CPRD when compared to CPRD-HES and the latter source was subsequently used. Calibration was good for both models with a slight over-prediction in the 10th percentile. There was marginal improvement in classification of hip fracture cases (1.24%) with a small deterioration in non-cases (0.24%), yielding an NRI of 0.01 (95% CI: 0.00, 0.02). There was no difference in C-statistics (0.87 versus 0.87).

Conclusion: The extension of FRAX predictors with psychotropic drug classes and glucocorticoid dose did not increase predictive performance for the 10-year risk of hip fracture.

INTRODUCTION

Hip fractures are associated with increased mortality, disability, pain, institutionalization, a decreased quality of life, and high healthcare costs.[1-4] And importantly, a substantial increase of this burden has been projected for the upcoming decades due to the ageing of the population.[5] Because of these consequences it is important to identify those at an increased risk of hip fracture to target effective interventions.

Although osteoporotic bone mineral density (BMD), defined as DXA-derived BMD ≥ 2.5 standard deviations below the average value for young women, is a major risk factor for fracture, its sensitivity for identifying patients at high risk of fracture is insufficient.[6] Indeed, the majority of fractures occur in individuals with a BMD value in the osteopenic range (BMD T-score: -1 to -2.5) so many individuals at risk for fracture remain undetected when only focusing on BMD.[6,7] Bone micro architectural properties, which remain unrevealed by DXA, and several clinical risk factors contribute to fracture risk independently of BMD. This has led to the development of fracture risk prediction models that incorporate clinical risk factors with or without BMD.[8-11] The FRAX algorithm, which was developed by the World Health Organization (WHO), is the most widely used tool for predicting the 10-year risk of hip and major osteoporotic fracture (hip, clinical spine, forearm, humerus).[8] It has been incorporated into clinical guidelines worldwide.[12-16] The clinical risk factors that are included are age, sex, weight, height, prior fracture, parental history of hip fracture, current smoking, excessive alcohol use, use of glucocorticoids, rheumatoid arthritis, secondary osteoporosis, and optionally BMD of the femoral neck.

FRAX has been critiqued since it takes no account of prior exposure or dose-responses for several risk factors.[17] Use of glucocorticoids has been included as a dichotomous variable while a dose-response mechanism for risk of (hip) fracture has been demonstrated previously.[18,19] Furthermore, psychotropic drugs are frequently used and several meta-analyses have shown increased risks of (hip) fracture following exposure to a variety of psychotropic drug classes including anxiolytics/hypnotics,[20] antidepressants,[21,22] antipsychotics,[22] and anticonvulsants.[23] Another downside of FRAX is its lack of transparency since the coefficients of the individual FRAX predictors were not published.[24] Although individual absolute fracture risks can be calculated simultaneously for large groups by a paid web-based FRAX algorithm, which enables recalibration of FRAX to a new population, it is impossible to determine the association of a new predictor with the already included individual predictors upon extension of FRAX.

Therefore, the aims of this study were to develop a prediction model for the 10-year risk of hip fracture with FRAX predictors and to determine whether extension of this model with psychotropic drug classes and glucocorticoid dose could increase predictive performance.

METHODS

DATA SOURCE AND STUDY POPULATION

We conducted a population-based cohort study within the Clinical Practice Research Datalink (CPRD) (the former General Practitioner Research Database, www.cprd.com). This database contains computerised medical records of 625 primary care practices in the United Kingdom, representing 8% of the total population. Data recorded in the CPRD includes demographic information, laboratory tests, primary care diagnoses, specialist referrals, hospital admissions, prescription details, and lifestyle variables such as body mass index (BMI), smoking, and alcohol consumption. Previous studies have shown a high validity of hip fracture registration (> 90% of fractures were confirmed),[25] and high degrees of accuracy and completeness of data have been shown for other diagnoses and mortality.[26-29] Linkage of CPRD data to Hospital Episode Statistics (HES; CPRD-HES) was eligible for 62% of the population captured within CPRD, who are all residing in England. Linkage to HES provides all hospital admissions including the date of discharge and the cause as defined by the International Classification of Disease (ICD) coding system. Approval for this study was given by ISAC for MHRA Database Research (protocol number 15_024A).

We selected a random sample of patients from CPRD and performed linkage to HES for eligible patients. The included population was restricted to an age between 40 and 90 years, since this is the age range over which FRAX predicts fracture risk. The start of valid data collection was the latest of the following dates; date a patient became 40 years old, date of registration within the practice, date on which the general practice computer system was included into CPRD, or the beginning of the study period at 1 April 1997 (in both CPRD and CPRD-HES). The end date of valid data collection was the earliest of the following dates; date of first recorded hip fracture during follow-up, date of death, date of transferring out of the practice, or study end date (maximum of 10 years after start of follow-up, 31 March 2014 the latest in both CPRD and in CPRD-HES). All patients should have had at least one year of valid data collection in their medical record before the start of follow-up. In line with the development criteria of FRAX, patients were excluded when they were exposed to any anti-osteoporosis drug (AOD; bisphosphonates, raloxifene, strontium ranelate, denosumab, parathyroid hormone) ever before the start of follow-up.

OUTCOMES

The occurrence of hip fracture was measured between the start of follow-up and death, end of the study period, or moving out of the CPRD, whichever came first. Hip fractures were ascertained by medical codes in CPRD, and solely by ICD-10 codes (S72.0, S72.1, and S72.2) in CPRD-HES. For patients with more than one hip fracture during follow-up, analyses were based upon time to the first fracture.

DEFINITION OF PREDICTORS

In records before the start of follow-up FRAX predictors were determined. These are age at start of follow-up (40 – 90 years), sex, body mass index (most recent value, < 18.5 kg/m^2, 18.5 – 25 kg/m^2, ≥ 25 kg/m^2), previous fracture at any site (ever before, yes/no), smoking status (most recent value, yes/no), alcohol use (most recent medical code for alcohol abuse or a medical code for alcohol use where the daily number of units was at least 3, yes/no), oral glucocorticoid use (prescription within 90 days before or ≥ two prescriptions with a mean daily dose of prednisolone [equivalents] of ≥ 5 mg in the year before, yes/no), rheumatoid arthritis (ever before, yes/no)[30], secondary osteoporosis (ever before, medical code for any of the following: type 1 diabetes mellitus, osteogenesis imperfecta, hypogonadism, premature menopause, malnutrition or malabsorption, and chronic liver disease, yes/no). A parental history of hip fracture was not available. Furthermore, oral glucocorticoid use was alternatively defined by mean daily dose (< 2.5 mg/day, 2.5 – 7.5 mg/day, > 7.5 mg/day)[18,19] in the year before. Finally, having received > 1 prescription for antidepressants (TCA, SSRI, and others combined), anti-convulsants, anxiolytics/hypnotics, and antipsychotics (typical/atypical combined) in the six months before were included as potential predictors.

Missing values for body mass index (height/weight), smoking status and alcohol use were imputed by multiple imputation using all predictors and the outcome variable, resulting in 5 imputed datasets.

STATISTICAL ANALYSES

Annual incidence rates of hip fracture and their 95% Confidence Intervals (95% CIs) were calculated by 5-year age categories in CPRD and in CPRD-HES. Fine and Gray regression analysis was used to comply with the outcome definition of FRAX where fracture risk is adjusted for mortality risk (i.e. sustaining a hip fracture within remaining lifetime up to 10 years).[31] Beta-coefficients and Hazard Ratios (HRs, also termed 'subdistribution HRs') were calculated for each predictor and for each imputed dataset and were combined using Rubin's rules. The Fine and Gray model allows prediction of an individual's 10-year risk of hip fracture for each set of patient characteristics by combining the baseline hazard with the beta-coefficients of the predictors. A base model was fitted with the FRAX predictors. The extended model included FRAX predictors, psychotropic drug classes and glucocorticoid dose categories. All predictors, except for age, were included as categorical variables. We investigated possible statistical interactions of the predictors with age and sex. The observed 10-year risk of hip fracture was estimated by the cumulative incidence function (CIF, %) instead of regular Kaplan-Meier analysis, to account for mortality risk and loss of follow-up, which adheres to the FRAX definition of the outcome.

The added predictive value of glucocorticoid dose and psychotropic drugs in addition to the FRAX predictors was examined in terms of the C-statistic and Net Reclassification

Improvement (NRI). The NRI is a more sensitive measure for determining differences in performance between prediction models and is targeted at evaluating the potential of a new predictor to change risk strata and therefore to alter treatment decisions.[32,33] The NRI was updated for survival analyses with competing risks[34,35] and was displayed separately for cases (those who sustained a hip fracture) and non-cases (those who did not sustain a hip fracture). Positive NRI values indicate adequate reclassification of risk, whereas negative values indicate inadequate reclassification of risk. We have calculated a category-based NRI using age-specific intervention thresholds for hip fracture as set by the UK National Osteoporosis Guideline Group (NOGG) which are linked to FRAX output in the UK for clinical decision making.[36] Bootstrapping (500 repetitions) was performed to internally validate the prediction models, where the C-statistics were adjusted for optimism and 95% CIs were calculated for the NRI [37]. All statistical analyses were performed in SAS 9.4 (SAS, Cary NC, USA). A p-value of < 0.05 was considered statistically significant.

RESULTS

Out of a random sample of 1 million patients from the UK CPRD, 312 331 were eligible for analysis. The excluded population was either < 40 or > 90 years old or had less than one year of valid data collection (n=682 454), or was prescribed any anti-osteoporosis drug ever before the start of follow-up (n=5215). Of those included, 193 516 patients were eligible for linkage to HES. Table 1 shows the baseline characteristics of both study populations. The median period of follow-up was similar in CPRD and in CPRD-HES (6.7 versus 6.6 years), during which there were 2299 (0.7%) and 2047 (1.1%) patients who sustained a hip fracture, respectively.

Table 2 shows the annual incidence of hip fracture in CPRD and in CPRD-HES. Overall, hip fracture incidence was significantly lower in CPRD (IR per 10 000 person-years: 12.0, 95% CI: 11.5–12.5) when compared to CPRD-HES (IR 17.3, 95% CI: 16.5 – 18.0). When stratified by 5-year age categories, this difference was observed from the age of 60 years. Due to the significantly lower hip fracture incidence in CPRD, the prediction models were developed and evaluated in CPRD-HES.

TABLE 1 | Characteristics of the study population in CPRD and in CPRD – HES.

Characteristic	CPRD (n=312 331)	CPRD – HES (n=193 516)
Median follow-up time, years (IQR)	6.7 (2.8 – 10.0)	6.6 (2.7 – 10.0)
Sex, n (%)		
Male	154 779 (49.6)	95 931 (49.6)
Female	157 552 (50.4)	97 585 (50.4)
Age, years, median (IQR)	51 (41 – 64)	51 (41 – 64)
Body mass index, kg/m^2, mean (± SD)	26.6 (5.1)	26.5 (5.1)
Missing	80 674 (25.8)	47 696 (24.6)
Current smoking, n (%)	58 340 (18.7)	36 019 (18.6)
Missing, n (%)	49 936 (16.0)	29 241 (15.1)
Alcohol use ≥ 3 units per day, n (%)	25 640 (8.2)	16 251 (8.4)
Missing, n (%)	78 130 (25.0)	46 702 (24.1)
Previous fracture, n (%)	52 947 (17.0)	32 257 (16.7)
Glucocorticoid use as in FRAX*, n (%)	4600 (1.5)	2921 (1.5)
Glucocorticoid use**, n (%)	4316 (1.4)	2692 (1.4)
< 2.5 mg/day	1994 (0.6)	1217 (0.6)
2.5 – 7.5 mg/day	1692 (0.5)	1074 (0.6)
> 7.5 mg/day	630 (0.2)	401 (0.2)
Secondary osteoporosis, n (%)	8607 (2.8)	5318 (2.7)
Rheumatoid arthritis, n (%)	1449 (0.5)	897 (0.5)
Antidepressants use, n (%)	24 289 (7.8)	14 793 (7.6)
Anti-convulsants use, n (%)	4064 (1.3)	2601 (1.3)
Anxiolytics/hypnotics use, n (%)	12 341 (4.0)	7124 (3.7)
Antipsychotics use, n (%)	3886 (1.2)	2390 (1.2)

Abbreviations: IQR; Interquartile Range, SD; standard deviation.
*Glucocorticoid use was defined as in FRAX: prescription within 90 days before or ≥ two prescriptions with a mean daily dose of prednisolone (or equivalents) of ≥ 5 mg in the year before.
** Glucocorticoid use was defined as ≥ two prescriptions with a mean daily dose of prednisolone (or equivalents) of < 2.5 mg/day, 2.5 – 7.5 mg/day or > 7.5 mg/day in the year before

TABLE 2 | Annual incidence rates of hip fracture in CPRD and in CPRD-HES*, by age category

	CPRD			CPRD - HES		
	N	IR**	95% CI	N	IR**	95% CI
Total	2299	12.0	11.5–12.5	2047	17.3	16.5–18.0
By age category						
40 – 44	16	0.5	0.3–0.8	13	0.7	0.3–1.0
45 – 49	39	1.2	0.8–1.6	24	1.2	0.7–1.6
50 – 54	40	1.6	1.1–2.1	27	1.7	1.1–2.4
55 – 59	71	3.0	2.3–3.7	46	3.2	2.3–4.1
60 – 64	99	4.8	3.9–5.8	83	6.6	5.2–8.0
65 – 69	140	8.2	6.9–9.6	110	10.5	8.5–12.5
70 – 74	210	14.6	12.6–16.6	182	20.5	17.5–23.4
75 – 79	382	32.1	28.9–35.3	324	43.9	39.1–48.7
80 – 84	519	60.6	55.3–65.8	445	83.3	75.6–91.1
85 – 89	521	104.4	95.4–113.3	537	172.7	158.1–187.3
90+	262	137.1	120.5–153.7	256	215.8	189.3–242.2

Abbreviations: IR; Incidence Rate, 95% CI; 95% Confidence Interval
*In CPRD hip fractures were extracted by medical codes, in CPRD-HES hip fractures were extracted by ICD-10 codes.
**Annual incidence rate per 10 000 person-years, averaged over the study period (1997 – 2014).

Table 3 shows beta-coefficients and HRs for the base model with FRAX predictors and the extended model with FRAX predictors, glucocorticoid dose and psychotropic drugs. All predictors, with the exception of secondary osteoporosis and glucocorticoid use/dosage, showed a significant association with the 10-year risk of hip fracture. Secondary osteoporosis and exposure to glucocorticoids were however retained in the models, as they are included in the FRAX algorithm. None of the interaction terms were subsequently added to the models.

TABLE 3 | Prediction models for 10-year risk of hip fracture adjusted for mortality risk

	Base model		Extended model	
	β (95% CI)	HR (95% CI)	β (95% CI)	HR (95% CI)
Female (ref: male)	0.61 (0.51–0.71)	1.83 (1.66–2.03)	0.58 (0.48–0.68)	1.79 (1.62–1.97)
Age, per year increase	0.10 (0.10–0.11)	1.11 (1.10–1.11)	0.10 (0.10–0.11)	1.11 (1.10–1.11)
BMI < 18.5 kg/m^2 (ref: 18.5–25 kg/m^2)	0.25 (-0.02–0.53)	1.29 (0.98–1.70)	0.24 (-0.03–0.52)	1.27 (0.97–1.67)
BMI ≥ 25 kg/m^2 (ref: 18.5–25 kg/m^2)	-0.28 (-0.41–-0.15)	0.76 (0.66–0.86)	-0.28 (-0.42–-0.15)	0.75 (0.66–0.86)
Fracture, ever before (yes/no)	0.48 (0.38–0.58)	1.62 (1.46–1.79)	0.46 (0.36–0.56)	1.59 (1.43–1.76)
Secondary osteoporosis, ever before (yes/no)	0.17 (-0.10–0.43)	1.18 (0.91–1.54)	0.12 (-0.14–0.39)	1.13 (0.87–1.48)
Rheumatoid arthritis, ever before (yes/no)	0.60 (0.21–0.98)	1.82 (1.24–2.68)	0.59 (0.19–0.98)	1.80 (1.21–2.66)
Alcohol use ≥ 3 units per day, ever before (yes/no)	0.48 (0.30–0.67)	1.62 (1.35–1.95)	0.47 (0.29–0.66)	1.61 (1.33–1.94)
Smoking, current (yes/no)	0.25 (0.15–0.36)	1.29 (1.16–1.43)	0.25 (0.14–0.35)	1.28 (1.15–1.43)
Glucocorticoid use (yes/no)*	0.18 (-0.06–0.41)	1.19 (0.95–1.51)	-	-
Glucocorticoid use of 2.5 – 7.5 mg/day (yes/no)**	-	-	0.21 (-0.12–0.54)	1.24 (0.89–1.72)
Glucocorticoid use of ≥ 7.5 mg/day (yes/no)**	-	-	-0.03 (-0.70–0.64)	0.97 (0.50–1.89)
Antidepressant use, six months before (yes/no)	-	-	0.19 (0.05–0.33)	1.21 (1.05–1.39)
Anticonvulsant use, six months before (yes/no)	-	-	0.62 (0.35–0.89)	1.87 (1.42–2.45)
Antipsychotic use, six months before (yes/no)	-	-	0.29 (0.05–0.53)	1.33 (1.05–1.70)
Hypnotics/sedatives, six months before (yes/no)	-	-	0.16 (0.01–0.30)	1.17 (1.01–1.35)

Abbreviations: β; Beta coefficients, HR; hazard ratios, BMI; body mass index.
*Glucocorticoid use as defined in FRAX: prescription within 90 days before or ≥ two prescriptions with a mean daily dose of prednisolone [equivalents] of ≥ 5 mg in the year before.
**Glucocorticoid use defined as ≥ two prescriptions with a mean daily dose of prednisolone [equivalents] of < 2.5 mg, 2.5 – 7.5 mg, or ≥ 7.5 mg in the year before; reference is no use or less than 2.5 mg/day.

Predicted risks agreed well with those observed across the percentiles of predicted risk, but a slight overestimation was observed for the highest percentile for both the base model (mean predicted 9.5%, observed 8.9%, 95% CI: 8.4–9.4) and the extended model (mean predicted 9.6%, observed 9.1%, 95% CI: 8.6–9.5) (Figure 1a and Figure 1b, respectively). The C-statistics were 0.87 for both models.

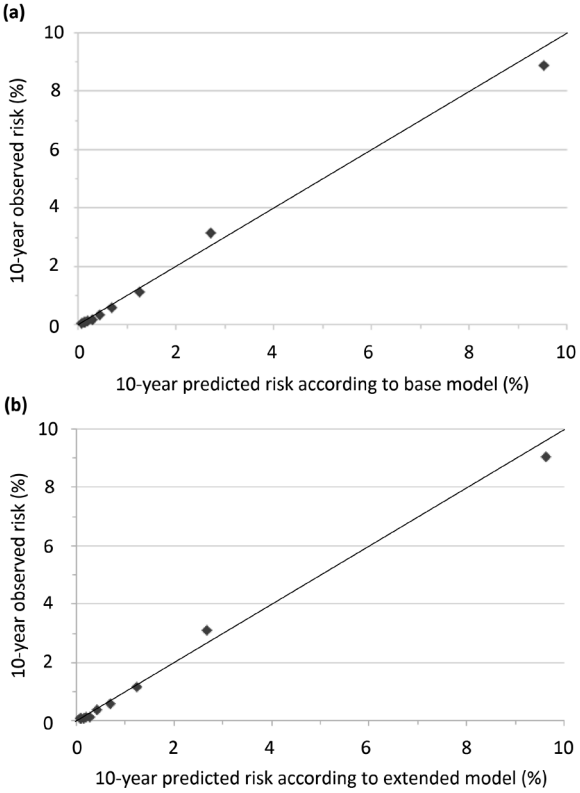

FIGURE 1 | Calibration of (a) base model and (b) extended model for 10-year risk of hip fracture, by percentiles of predicted risk

Extension of the base model with psychotropic drug classes and glucocorticoid dose resulted in minimal net reclassification of hip fracture cases and non-cases (Table 4). The net correct classification of hip fracture cases improved by 1.24% (95%: 1.23 – 1.25), while there was a small loss of 0.24% (95% CI: 0.24 – 0.24) for net correct classification of non-cases, yielding an NRI of 0.01 (95% CI: 0.00 – 0.02).

TABLE 4 | Reclassification of hip fracture cases and non-cases with addition of psychotropic drug classes and glucocorticoid dose to FRAX predictors, using age-specific NOGG intervention thresholds*

Base model**	Extended model***			
	Increased risk category	Same risk category	Decreased risk category	Total
Total, n	1207	191 604	705	193 516
Hip fracture cases, n	113	3024	73	3210
Hip fracture non-cases, n	1094	188 580	632	190 306

*The intervention threshold is set at the probability of hip fracture equal to that of a woman, with BMI 24 kg/m^2, and prior fracture, for a specific year of age and is applied to both men and women.
**Base model includes risk factors as in FRAX without parental history of hip fracture
*** Extended model includes risk factors as in FRAX without parental history of hip fracture, and was extended with glucocorticoid dose (<2.5 mg/day, 2.5 – 7.5 mg/day, >7.5 mg/day) and with psychotropic drug classes (antidepressants, anticonvulsants, antipsychotics, and anxiolytics/hypnotics)

DISCUSSION

The extension of FRAX predictors with glucocorticoid dose and psychotropic drugs did not increase predictive performance for the 10-year risk of hip fracture. There was only minimal reclassification of hip fracture cases and non-cases, which has no significant impact on clinical decision making. The C-statistics were good for both models and did not differ. Furthermore, we observed significant underestimation of hip fracture incidence in primary care data.

In contrast to previous literature, this study does not report a dose-response relationship for exposure to oral glucocorticoids and the risk of hip fracture.[18,19] There are several possible explanations. First, exposure status was measured at baseline and not during follow-up, and second previous studies used Cox regression while the current study used Fine and Gray regression. Fine and Gray regression has been advocated for predictive modelling with competing risks.[31,38] The hazard function is then defined as the risk of hip fracture given that an individual has survived up to time *t* without hip fracture *or* has died prior to time *t*.[31] A higher competing risk of death would therefore result in a lower hazard ratio. Indeed, glucocorticoid use has previously been associated with a dose-dependent increase in mortality.[39,40]

The lack of a dose response relationship for exposure to glucocorticoids and 10-year risk of hip fracture does not support guidance from Kanis et al.[41] which advocates adjustment of the predicted FRAX risk with glucocorticoid dose where the risk of hip fracture should be decreased by 35% for low-dose exposure (< 2.5 mg/day) and increased by 20% for high-dose exposure (> 7.5 mg/day). They applied the dose response relationship that was previously observed in the General Practice Research Database (now CPRD) to re-estimate the relative risk for glucocorticoid exposure that was previously implemented in FRAX. Assumptions were made for a dose-response on the death hazard. However, this study was not based on individual patient data, and could therefore not directly assess the influence of dose responses

of glucocorticoids on fracture risk and mortality risk simultaneously. And, most importantly, it was not assessed whether this guidance resulted in reclassification of predicted risk among hip fracture cases and non-cases.

We are not aware of other studies that have estimated associations between psychotropic drug classes and hip fracture risk where mortality risk was taken into account. These drugs were used in a reasonable large proportion of the study population and showed a moderate association with hip fracture risk after adjustment for mortality risk. A possible explanation for the lack of improvement in reclassification of predicted risk upon inclusion of these drugs may be the long timespan over which hip fracture risk was predicted. The exposure status was assessed at baseline but could very likely have changed in individual patients during follow-up. It should also be noted that NRI results depend on the choice of intervention thresholds. We have applied age-specific intervention thresholds that were set by the UK NOGG that are currently linked to the output of the UK FRAX algorithm for clinical decision making.[36] Results may not be extrapolated to countries that incorporate a fixed intervention threshold for all patients and where absolute fracture risk may differ.

Qfracture is an alternative prediction model for fracture risk, and is recommended in NICE guidance next to FRAX. Qfracture does not take mortality risk into account. This will result in higher predicted risks from Qfracture as compared to FRAX, especially when the mortality risk increases (e.g. with increasing age). Qfracture was derived from the UK primary care database Q-research and was validated in other primary care databases including THIN and CPRD.[9,42,43] It performed excellent with good discrimination and calibration. The present study, however, showed a significant underestimation of hip fracture incidence in CPRD when compared to CPRD-HES (hospitalisation data). The under ascertainment of hip fractures may also be found in Q-research since hip fracture incidence has been reported to be similar in Q-research and in GPRD.[9,44] Predicted risks from Qfracture should therefore be interpreted with caution, where predicted risks may be an underestimate of the true risk. This warrants further external validation of Qfracture in a prospective study with reliable fracture ascertainment or after linkage of primary care data to hospitalizations.

A particular strength of this study is its prospective cohort design which captures a large representative population in the United Kingdom. Because of linkage to hospitalisation data, absolute risks of hip fracture were reliably estimated. Furthermore, previous studies that have evaluated the added predictive value of other predictors in addition to FRAX predictors or that compared performance between prediction models mostly relied on differences in C-statistics.[11,45,46] We used the NRI statistic which is a more sensitive method for determining differences in predictive performance between models, and is relevant for determining the impact on clinical decision making. There are also several limitations that should be considered in the interpretation of our results. The output of the prediction models was 10-year risk of

hip fracture, but not all patients had 10 years of follow-up. Furthermore, prediction models did not include BMD and a parental history of hip fracture. We were also not able to include the number of previous fractures as a predictor variable due to the likely under recording of fractures in CPRD. This restricted us from performing this study for the 10-year risk of major osteoporotic fracture, which is also an outcome from FRAX.

In conclusion, we demonstrated that extension of FRAX predictors with psychotropic drug classes and glucocorticoid dose did not increase predictive performance for the 10-year risk of hip fracture.

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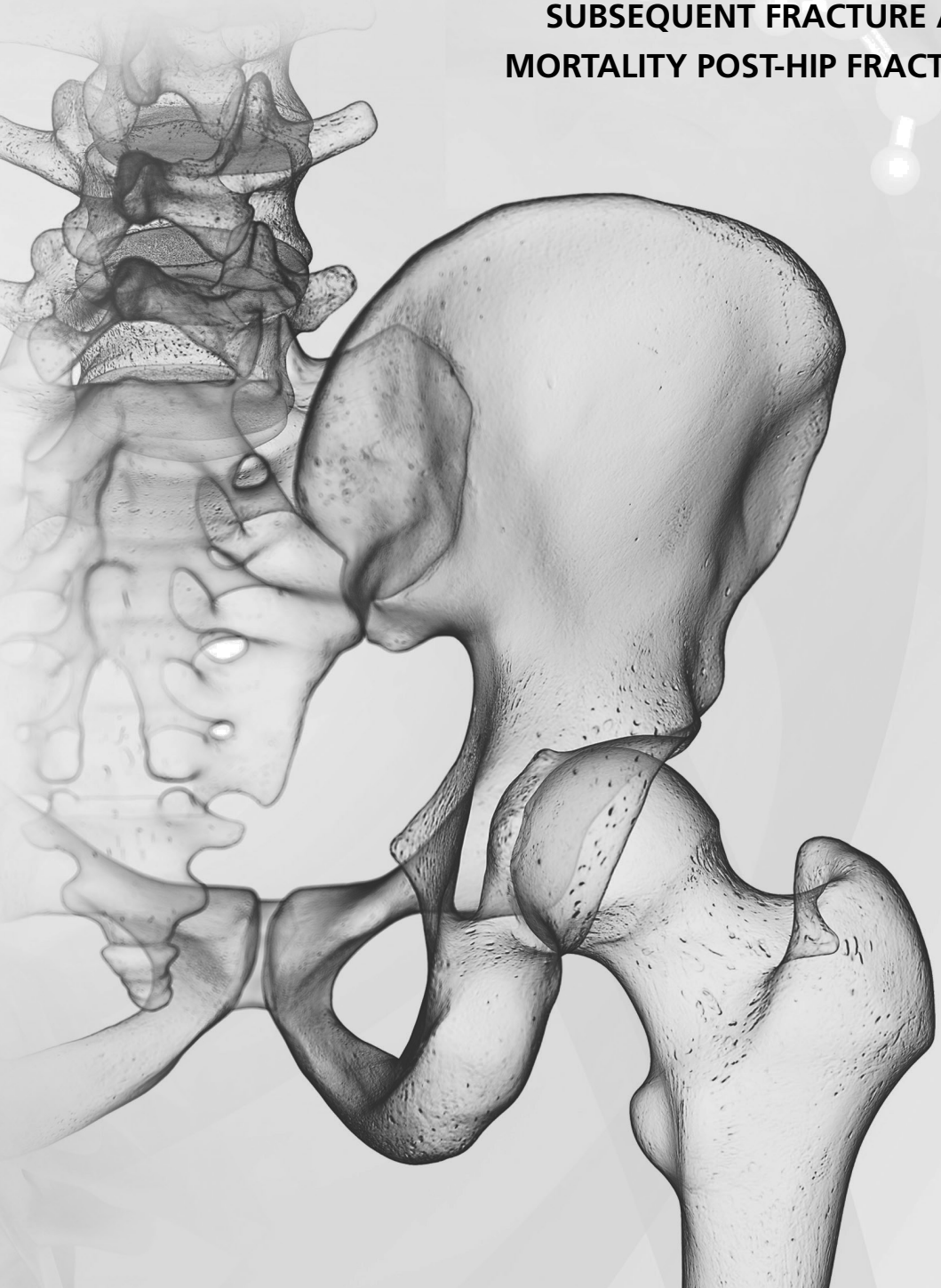
CHAPTER 3

SUBSEQUENT FRACTURE AND MORTALITY POST-HIP FRACTURE



CHAPTER 3.1

The risk of major and any (non-hip) fragility fracture after hip fracture in the United Kingdom: 2000-2010

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ABSTRACT

Summary: The risk of a subsequent major or any fracture after a hip fracture and secular trends herein were examined. Within 1 year, 2.7% and 8.4% of patients sustained a major or any (non-hip) fracture, which increased to 14.7% and 32.5% after 5 years. Subsequent fracture rates increased during the study period both for major and any (non-hip) fracture.

Introduction: Hip fractures are associated with subsequent fractures, particularly in the year following initial fracture. Age-adjusted hip fracture rates have stabilized in many developed countries, but secular trends in subsequent fracture remain poorly documented. We thus evaluated secular trends (2000–2010) and determinants for the risk of a subsequent major (humerus, vertebral, or forearm) and any (non-hip) fracture after hip fracture.

Methods: Patients ≥ 50 years with a hip fracture between 2000 and 2010 were extracted from the UK Clinical Practice Research Datalink (n = 30 516). Incidence rates, cumulative incidence probabilities, and adjusted hazard ratios (aHRs) were calculated.

Results: Within 1 year following hip fracture, 2.7% and 8.4% of patients sustained a major or any (non-hip) fracture, which increased to 14.7% and 32.5% after 5 years, respectively. The most important risk factors for a subsequent major fracture within 1 year were the female gender (aHR 1.90, 95% confidence interval (CI) 1.51–2.40) and a history of secondary osteoporosis (aHR 1.54, 95% CI 1.17–2.02). The annual risk increased during the study period for both subsequent major (2009–2010 vs. 2000–2002: aHR 1.44, 95% CI 1.12–1.83) and any (non-hip) facture (2009–2010 vs. 2000–2002: aHR 1.80, 95% CI 1.58–2.06).

Conclusion: The risk of sustaining a major or any (non-hip) fracture after hip fracture is small in the first year. However, given the recent rise in secondary fracture rates and the substantial risk of subsequent fracture in the longer term, fracture prevention is clearly indicated for patients who have sustained a hip fracture.

INTRODUCTION

Osteoporosis frequently results in fragility fractures: fractures caused by a low energy trauma such as a fall from standing height. A hip fracture is the most serious fragility fracture as it nearly always requires hospitalisation, is fatal in 20% of cases,[1] and leaves 29% of subjects permanently disabled.[2] Additionally, many studies have shown that an initial hip fracture greatly increases the risk of a subsequent fracture.[3] A meta-analysis by Klotzbuecher *et al.*[4] found that a history of hip fracture increased the risk of a future fracture by 2 to 2.5 times. In 2011, this figure was updated by Warriner *et al.*[5] who, after the inclusion of six extra studies, found a relative risk of 3.2 for subsequent fracture following a hip fracture. Further analysis has shown that this risk is most prominent in the first year following an initial fracture[6-8] and persists for 5 years[9,10] after the initial hip fracture. The impact of a second hip fracture on mobility, social independence, and mortality appears even greater than that of the first hip fracture.[11-13]

Studies into hip fracture trends have shown that, in the UK, age- and sex-specific rates increased steadily until 1979–1985, after which they plateau.[14] Moreover, since the turn of the century some studies have shown a small decline.[15,16] Furthermore, the age of first hip fracture has increased with the general aging of the population.[14,17] Another factor which could influence secondary fracture rates is the use of bisphosphonates which are recommended by UK clinical guidelines for patients suffering an initial hip fracture.[18] Although two studies[19,20] have investigated whether the levelling of (age-adjusted) hip fracture rates also applies to subsequent hip fractures, there are no studies that compare the trends in other types of fracture. According to the World Health Organisation (WHO), humerus, vertebrae, and forearm fractures, in conjunction with hip fractures, are classified as "major osteoporotic fractures",[21] and some studies consider any fracture in the elderly worthy of specific osteoporosis management. Therefore, the aim of this study is to evaluate the risk of both a major (humerus, vertebrae, and forearm [radius/ulna]) and any subsequent fracture after a hip fracture, including its determinants, and to determine secular trends for this risk between 2000 and 2010.

METHODS

SOURCE POPULATION

The population was sourced from the Clinical Practice Research Datalink (CPRD), which contains anonymized electronic health records representing about 8 % of the UK population. It includes details of prescriptions, specialist referrals, hospital admissions, medical history, and lifestyle variables such as body mass index (BMI) and smoking status. Previous studies have shown a high validity of hip fracture registration (> 90% of fractures were confirmed).[22]

STUDY POPULATION

The current study population included patients aged ≥ 50 years who suffered an incident hip fracture between 1 January 2000 and 31 December 2010. Patients with a record of non-specified fractures prior to the index hip fracture date were excluded. Data extraction was approved by the Independent Scientific Advisory Committee for British Medicines and Healthcare products Regulatory Agency (MHRA) database research (protocol number 13_113). Patients were followed from the index hip fracture date (baseline) to censoring (death, withdrawal from the database, or end of data collection [365 days after index hip fracture date, 31 December 2011 the latest]), whichever came first.

OUTCOME

The primary outcome of interest was the occurrence of a major (non-hip) fragility fracture, i.e., a fracture of the humerus, vertebrae, or forearm (radius and ulna) within 1 year following the incident hip fracture. These fractures, in conjunction with hip fractures, are classified as "major osteoporotic fractures" by the World Health Organization.[21] However, subsequent hip fractures were excluded from our outcome of interest because it is not possible within the CPRD to identify whether a general practioner (GP) consultation refers to a new or old fracture. Some expert panels have attributed additional fracture sites to osteoporosis.[23,24] Hence, a sensitivity analysis was performed using any fracture, also excluding hip fractures, as an outcome. All patients were followed from the index hip fracture date (baseline) to date of subsequent major (non-hip) or any (non-hip) fracture or censoring, whichever came first. In addition, fracture rates were also calculated by extending the follow-up period to 5 years after initial hip fracture.

DEFINITION OF COVARIATES

A multitude of potential risk factors have been associated with subsequent fragility fractures. General and lifestyle risk factors that affect bone mineral density included gender, age, body mass index, smoking status, and alcohol use. Included medical conditions which have been associated with an increased risk of fracture were a history of a major (non-hip) fracture, inflammatory bowel disease (Crohn's disease and ulcerative colitis), rheumatoid arthritis, Parkinson's disease, a history of falls, and the presence of secondary osteoporosis in accordance with the fracture risk assessment tool (FRAX) definition [anorexia nervosa, coeliac disease, diabetes mellitus (type 1), hypogonadism, osteogenesis imperfecta, osteomalacia, liver disease (cirrhosis, hepatitis and neoplasms), malnutrition, mal-absorption, and premature menopause].[17,21,25-27] There are several types of drugs that are associated with either an increased risk of falls or reduced bone mineral density. Hence, the following classes were included in the analyses: corticosteroids (systemic and inhaled), benzodiazepines and other sedatives and hypnotics, antipsychotics, antidepressants, narcotic analgesics stronger than tramadol, and anticonvulsants.[28,29] Finally, medications which may have a beneficial effect on osteoporosis progression were included in the following combinations: bisphosphonates,

strontium ranelate, calcitonin, and parathyroid hormone (PTH), hormone replacement therapy (HRT), and selective oestrogen receptor modulators (SERMs), and finally, vitamin D and calcium.[30]

Covariates for age, gender, BMI, smoking status, alcohol use, and history of fracture were assessed at baseline. Covariates for drugs and diseases were included on a time-dependent basis, i.e., medication use or disease occurrence before and during follow-up. The total follow-up time was divided into 30-day intervals starting at the date of index hip fracture. Drug prescriptions or medical history was then evaluated for the period prior to the start of each 30-day interval. An exposure window of ever-before was used for medical conditions, 6 months prior for drug prescriptions and occurrence 3–12 months before the interval date for falls.

STATISTICAL ANALYSIS

Gender-specific baseline characteristics were calculated for all variables using descriptive statistics. Baseline characteristics were also produced for patients who transferred out the CPRD or died within 1 year of the index hip fracture. Incidence rates for the 1-year risk of subsequent major (non-hip) and any (non-hip) fracture per 1,000 person-years were calculated for patients defined by different covariates. This was performed for the total study period (1 January 2000–31 December 2011) and stratified by year groups of initial hip fracture. The annual incidence rate per 1,000 person years for major (non-hip) and any (non-hip) fractures was illustrated for males and females. The cumulative incidence probability of subsequent major (non-hip) and any (non-hip) fracture within 1 year of hip fracture was estimated using Kaplan–Meier plots. Cumulative incidence probabilities and incidence rates per 1,000 person years for subsequent fracture were also calculated using a 5-year follow-up.

Cox regression analysis was used to estimate the contribution of covariates to the 1-year risk of subsequent major (non-hip) and any (non-hip) fracture within both univariate and multivariate models. In a sensitivity analysis, we applied Fine and Gray regression to determine the influence of competing mortality risk on the estimation of predictors of subsequent fracture.

Furthermore, we used Cox proportional hazard models to determine adjusted hazard ratios (HRs) stratified by year group of hip fracture, utilizing the years 2000–2002 as the reference category. Statistical significance was defined as a p value < 0.05.

Multiple imputations were used to correct for missing data in the covariates BMI, smoking status and alcohol use. Five imputations were made and analyses were performed separately for the five datasets before pooling the HRs (PROC MIANALYZE). All statistical analyses were performed in SAS version 9.2 (SAS, Cary NC, USA).

RESULTS

The study population consisted of 7349 males and 23 167 females whose median age (interquartile range) was 79 (71–85) and 83 (76–88) years, respectively. Of these, 655 suffered either a humerus, vertebrae, or forearm fracture, 6576 died and 2987 left the database within 1 year of sustaining a hip fracture. Comparison of baseline characteristics between those who died, left the CPRD or completed the 1-year follow-up can be found in the Table S1. The proportion of patients that sustained any (non-hip) fracture within a year was three times higher (2172 patients) than for major (non-hip) fragility fractures. During the 1-year follow-up the mean duration to subsequent major (non-hip) fragility fracture was 4.9 ± 3.6 months and the mean follow-up time was 0.8 ± 0.4 years. At baseline 2924 (9.6%) patients had received a prescription for bisphosphonates, strontium ranelate, calcitonin or PTH within the previous 6 months (Table 1).

INCIDENCE OF SUBSEQUENT MAJOR AND ANY (NON-HIP) FRAGILITY FRACTURE

Over the first year following the index hip fracture the incidence rate (IR) for sustaining any (non-hip) fracture was 95.4 per 1,000 person years (cumulative incidence probability; 8.4%), and 27.6 per 1,000 person years for major (non-hip) fragility fracture (either the humerus [11.0], forearm [13.0] or the vertebrae [4.1]; cumulative incidence probability 2.7%). In comparison, when events were evaluated over a 5-year period, based on a population of 15 964 patients, the incidence rate was 28.2 per 1,000 person years (cumulative incidence probability; 14.7%) for major (non-hip) fragility fractures and 70.0 per 1,000 person years (cumulative incidence probability; 32.5%) for any (non-hip) fracture.

DETERMINANTS OF 1-YEAR RISK OF SUBSEQUENT MAJOR AND ANY (NON-HIP) FRAGILITY FRACTURE

Multivariate Cox regression analyses revealed the largest adjusted hazard ratios (aHRs) for female gender (aHR 1.90; 95 % CI 1.51–2.40), a history of secondary osteoporotic diseases (aHR 1.54; 95 % CI 1.17–2.02), and a history of major fracture (aHR 1.47, 95 % CI 1.24–1.72) (Tables 2 and 3). Patients with a low BMI had a significantly increased fracture risk when compared to patients with a normal BMI (aHR 1.44; 95 % CI 1.09–1.91). Ex-smokers had no significantly increased risk whereas current smokers were at greater risk of fracture when compared to non-smokers (HR 1.28; 95 % CI 1.06–1.55) although this was no longer significant in the multivariate model. A history of falls (3–12 months prior to hip fracture), the presence of rheumatoid arthritis and consumption of alcohol did not appear to confer increased risk of subsequent major fracture. Determinants for any (non-hip) fracture were similar to those found for major (non-hip) fragility fractures with the exception of BMI which was no longer associated with increased the risk of fracture. Additionally, combined osteoporotic treatment showed a protective effect for any (non-hip) fracture.

TABLE 1 | Baseline characteristics of hip fracture patients included between 2000 and 2010

Characteristic	Male (n=7349)		Female (n=23 167)		Total (n=30 516)	
Age, n (%)						
50-59	555	(8)	820	(4)	1375	(5)
60-69	1045	(14)	1856	(8)	2901	(10)
70-80	2163	(29)	5680	(25)	7843	(26)
80-89	2951	(40)	10 861	(47)	13 812	(45)
90+	635	(9)	3950	(17)	4585	(15)
BMI [a] category (kg/m^2), n (%)						
< 18	636	(8.7)	3013	(13.0)	3649	(12.0)
18 - 25	2506	(34.1)	7306	(31.5)	9812	(32.2)
> 25	2569	(35.0)	6458	(27.9)	9027	(29.6)
Missing [b]	1638	(22.3)	6390	(27.6)	8028	(26.3)
Smoking category, n (%)						
Non-Smoker	2500	(34.0)	12 090	(52.2)	14 590	(47.8)
Ex-smoker	2167	(29.5)	3544	(15.3)	5711	(18.7)
Current Smoker	1959	(26.7)	4531	(19.6)	6490	(21.3)
Missing [b]	723	(9.8)	3002	(13.0)	3725	(12.2)
Alcohol category, n (%)						
Yes	1287	(17.5)	6141	(26.5)	7428	(24.3)
No	4675	(63.6)	11 460	(49.5)	16 135	(52.9)
Missing [b]	1387	(18.9)	5566	(24.0)	6953	(22.8)
Disease history, n (%)						
History of fragility fracture [c]	769	(17.5)	5140	(22.2)	5909	(19.4)
≥ 1 fall (3 – 12 months prior)	523	(7.1)	2097	(9.1)	2620	(8.6)
Secondary osteoporosis [d]	546	(7.4)	1221	(5.3)	1767	(5.8)
Inflammatory bowel disease [e]	101	(1.4)	266	(1.1)	367	(1.2)
Rheumatoid arthritis	187	(2.5)	925	(4.0)	1112	(3.6)
Parkinson's disease	380	(5.2)	660	(2.8)	1040	(3.4)
Drug history (in 6 month prior to hip fracture), n (%)						
Antipsychotic	456	(6.2)	1788	(7.7)	2244	(7.4)
Antidepressants	1394	(19.0)	5751	(24.8)	7145	(23.4)
Anti-epileptics	424	(5.8)	970	(4.2)	1394	(4.6)
Corticosteroids (systemic and inhaled)	572	(7.8)	1842	(8.0)	2414	(7.9)
Sedatives and hypnotics	657	(8.9)	3735	(16.1)	4392	(14.4)
Opioid analgesics	1358	(18.5)	4822	(20.8)	6180	(20.3)
Bisphosphonates, strontium ranelate, calcitonin and PTH	298	(4.1)	2626	(11.3)	2924	(9.6)
HRT [f,g] and SERMs [h]	3	(0.0)	274	(1.2)	277	(0.9)
Vitamin D and Calcium	562	(7.6)	3875	(16.7)	4437	(14.5)

[a] Body mass index
[b] Imputed values were used for regression models
[c] Fragility fracture: humerus. forearm, and vertebrae
[d] As defined by FRAX: anorexia nervosa, coeliac disease, diabetes mellitus (Type 1), hypogonadism, osteogenesis imperfecta, osteomalacia, liver disease (cirrhosis, hepatitis, and neoplasms), malnutrition, mal-absorption, and premature menopause
[e] Crohn's disease and ulcerative colitis
[f] Includes oestrogen treatment
[g] Hormone replacement therapy
[h] Selective oestrogen-receptor modulator

TABLE 2| Incidence rate and Cox proportional hazard ratios (95% confidence intervals) for all covariates affecting the 1-year risk of subsequent fracture for patients who had an initial hip fracture between 2000-2010 in the UK

	Major (non-hip) fragility fracture				Any (non-hip) Fracture			
	No. of fractures	IR	Crude HR [a] (95% CI)	Adjusted HR [b] (95% CI)	No. of fractures	IR	Crude HR [a] (95% CI)	Adjusted HR [b] (95% CI)
Overall	655	28.19			2172	70.15		
Age (years)								
50-59	23	18.57	1.00 (reference)	1.00	115	98.43	1.00 (reference)	1.00
60-69	49	18.83	0.99 (0.60-1.62)	0.98 (0.60-1.61)	238	96.22	0.97 (0.78-1.21)	0.97 (0.77-1.21)
70-79	208	31.57	1.56 (1.02-2.41)	1.60 (1.04-2.49)	601	95.23	0.92 (0.75-1.13)	0.94 (0.76-1.15)
80-89	303	29.12	1.37 (0.90-2.10)	1.45 (0.94-2.24)	959	95.86	0.88 (0.73-1.07)	0.91 (0.74-1.11)
90+	72	24.72	1.10 (0.69-1.76)	1.18 (0.73-1.92)	259	91.89	0.97 (0.63-0.98)	0.82 (0.65-1.03)
Gender								
Male	89	16.08	1.00 (reference)	1.00	433	81.41	1.00 (reference)	1.00
Female	566	31.08	1.94 (1.55-2.43)	1.90 (1.51-2.40)	1739	99.62	1.24 (1.11-1.37)	1.26 (1.13-1.41)
Body mass Index (kg/m^2) [c]								
< 18	63	44.97	1.53 (1.16-2.02)	1.44 (1.09-1.91)	161	120.0	1.17 (0.98-1.40)	1.14 (0.95-1.36)
18 - 25	324	27.27	1.00 (reference)	1.00	1105	96.94	1.00 (reference)	1.00
> 25	268	25.61	0.93 (0.77-1.14)	0.93 (0.76-1.14)	906	90.28	0.93 (0.84-1.03)	0.92 (0.83-1.03)

Smoking Status[c]								
Non-Smoker	343	26.29	1.00 (reference)	1.00	1160	92.64	1.00 (reference)	1.00
Ex-smoker	136	26.68	1.17 (0.93-1.46)	1.12 (0.89-1.41)	488	100.1	1.13 (1.00-1.27)	1.09 (0.97-1.23)
Current Smoker	176	31.42	1.28 (1.06-1.55)	1.20 (0.98-1.47)	524	97.38	1.05 (0.94-1.17)	1.00 (0.89-1.12)
Alcohol Use[c]								
No	219	26.53	1.00 (reference)	1.00	687	97.80	1.00 (reference)	1.00
Yes	436	27.46	0.97 (0.80-1.18)	0.94 (0.77-1.15)	1485	94.28	1.01 (0.91-1.12)	1.01 (0.90-1.12)

IR – Incidence rate (number of events per 1000 patient-years); HR – hazard ratio; 95% CI – 95% confidence interval
[a] Age- and sex-adjusted
[b] Adjusted for age, sex, body mass index, smoking status, alcohol use, disease history (ever recorded) and drug history (6 months prior)
[c] Missing values are imputed

TABLE 3 | Incidence rate and Cox proportional hazard ratios (95% CI) for drug and disease covariates affecting the 1-year risk of subsequent fracture for patients who had an initial hip fracture between 2000 and 2010 in the UK

	Major (non-hip) Fragility Fracture				Any (non-hip) Fracture			
	No. of fractures	IR	Adjusted HR [a] (95% CI)		No. of fractures	IR	Adjusted HR [a] (95% CI)	
Disease history [b]								
History of major fracture [c]	182	39.42	1.47	(1.24-1.72)	525	119.23	1.30	(1.17-1.72)
≥ 1 fall (3-12 months prior)	60	34.39	1.15	(0.93-1.42)	201	116.15	1.09	(0.96-1.24)
Secondary osteoporosis [d]	58	43.60	1.54	(1.17-2.02)	187	148.50	1.47	(1.26-1.71)
Inflammatory bowel disease [e]	8	27.17	0.92	(0.46-1.84)	30	105.88	1.05	(0.73-1.51)
Rheumatoid arthritis	32	34.70	1.12	(0.78-1.61)	90	101.46	1.01	(0.81-1.25)
Parkinson's disease	24	32.33	1.18	(0.79-1.79)	68	95.19	0.95	(0.74-1.21)
Drug history [b] (in 6 month prior)								
Antipsychotics	40	28.31	0.93	(0.68-1.26)	126	92.37	0.87	(0.73-1.03)
Antidepressants	178	33.44	1.16	(0.97-1.38)	570	112.10	1.16	(1.05-1.28)
Antiepileptics	39	35.42	1.40	(1.03-1.90)	123	117.54	1.22	(1.02-1.46)
Corticosteroids	71	39.41	1.40	(1.16-1.70)	432	112.28	1.22	(1.09-1.36)
Sedatives and hypnotics	147	35.06	1.06	(0.88-1.29)	441	109.68	1.07	(0.96-1.20)
Opioid analgesics	158	32.69	1.21	(1.02-1.44)	502	108.46	1.08	(0.98-1.19)
Osteoporosis treatment [f]	157	36.18	0.90	(0.76-1.06)	463	111.52	0.88	(0.80-0.97)
Bisphosphonates	85	36.43	0.89	(0.71-1.10)	225	114.41	0.94	(0.83-1.07)
HRT and SERMs	4	16.73	0.51	(0.19-1.38)	20	87.24	0.81	(0.52-1.26)
Vitamin D/calcium	125	36.45	0.93	(0.76-1.13)	376	114.80	0.91	(0.81-1.02)

IR – Incidence rate (number of events per 1000 patient years); HRT – hormone replacement therapy; SERM – selective oestrogen receptor modulator
[a] Adjusted for age, sex, body mass index, smoking status, alcohol use, disease history (ever recorded) and drug history (6 months prior)
[b] Reference category is a healthy subject /non user
[c] Major fracture: humerus. forearm, and vertebrae
[d] Anorexia nervosa, coeliac disease, diabetes mellitus type I, hypogonadism, osteogenesis imperfecta, osteomalacia, liver disease (cirrhosis, hepatitis, and neoplasms), malnutrition, mal-absorption, premature menopause
[e] Crohn's disease and ulcerative colitis
[f] Bisphosphonates, strontium ranelate, calcitonin, hormone replacement therapy, selective estrogen-receptor modulators, vitamin D/calcium
[h] Hormone replacement therapy
[i] Selective estrogen-receptor modulator

TABLE 4 | Cox proportional hazard ratios (95% CI) for the 1-year risk of subsequent fracture grouped according to year of first hip fracture

	Major (non-hip) Fragility Fracture				Any (non-hip) Fracture			
Year period	No. of fractures	IR	Fully Adjusted HR (95% CI) [a]		No. of fractures	IR	Fully Adjusted HR (95% CI) [a]	
2000-2002	143	26.38	1.00 (reference)		433	82.69	1.00 (reference)	
2003-2005	199	28.17	1.09	(0.87-1.35)	547	79.87	0.98	(0.86-1.11)
2006-2008	169	23.81	0.95	(0.77-1.20)	637	93.42	1.16	(1.02-1.31)
2009-2010	144	34.60	1.44	(1.12-1.83)	555	142.32	1.80	(1.58-2.06)

IR – Incidence rate (number of events per 1000 patient years); HR – hazard ratio; 95% CI – 95% confidence interval
[a] Adjusted for age, sex, body mass index, smoking status, alcohol use, disease history (ever recorded) and drug history (6 months prior)

Cox regression revealed age between 70 and 79 years as a significant risk factor for subsequent major (non-hip) fracture as compared to the age of 50–59 years. However, in sensitivity analyses where mortality was taken into account as a competing risk, there was no such effect for age. Adjusted HRs for subsequent major (non-hip) fracture were not significantly different between age categories taking age of 50–59 years as the reference (60–69 years: adj. HR 0.95, 95 % CI 0.58–1.57; 70–79 years: adj. HR 1.50, 95 % CI 0.97–2.32; 80–89 years: adj. HR 1.28, 95 % CI 0.83–1.97; 90+ years: adj. HR 0.92, 95 % CI 0.57–1.49). For any (non-hip) fracture, the adjusted HRs were as follows: 60–69 years: adj. HR 0.95, 95 % CI 0.76–1.19; 70–79 years: adj. HR 0.88, 95 % CI 0.71–1.08; 80–89 years: adj. HR 0.81, 95 % CI 0.66–0.99; and 90+ years: adj. HR 0.66, 95 % CI 0.52–0.83. In contrast to age, sensitivity analyses yielded similar HRs for all other covariates and revealed the same significant predictors for subsequent fracture as was estimated by Cox regression (data were taken from Tables S2 and S3).

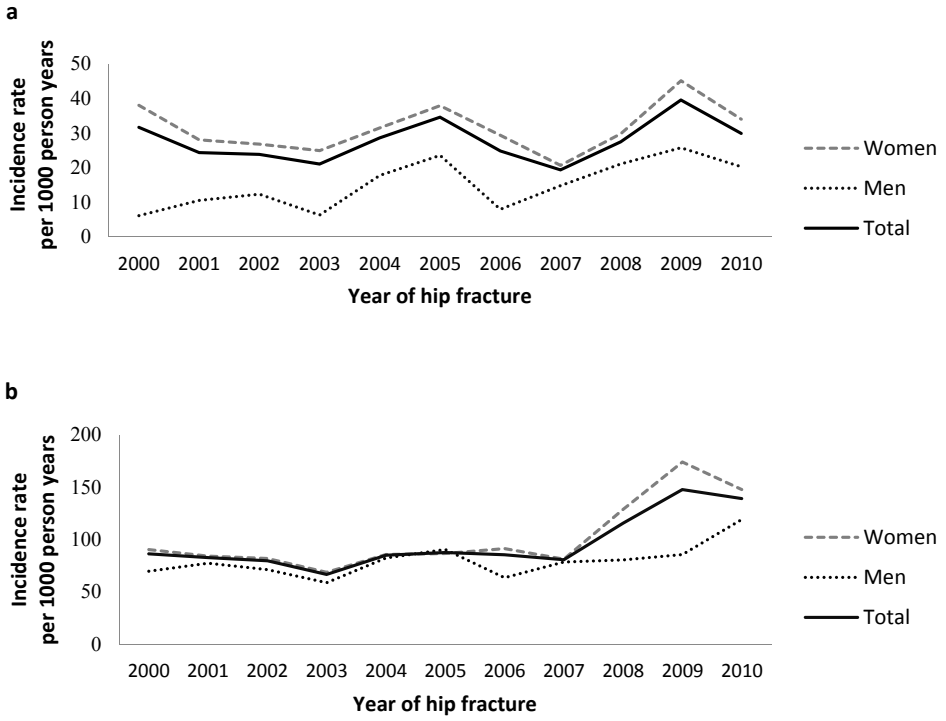

FIGURE 1 | Incidence rates (per 1000 person years) of (a) major (non-hip) fragility fracture and (b) any (non-hip) fractures by calendar year

SECULAR TRENDS IN 1-YEAR RISK OF SUBSEQUENT FRACTURE, 2000-2010

The crude 1-year IR of subsequent major (non-hip) fragility fracture remained relatively stable over the period 2000–2008 with a slight increase in the period 2009–2010 (Figure 1). This pattern was also seen after statistical adjustments, for 2009–2010 vs. 2000–2002 (adj. HR

1.44, 95 % CI 1.12–1.83; Table 4). The trends for any (non-hip) fracture were similar to those of the major (non-hip) fragility fracture with a stable crude incidence rate between 2000 and 2007, after which the rate rose sharply (Figure 1). In both periods 2006–2008 and 2009–2010, risk of subsequent fracture appeared greater than in 2000–2002 (Table 4).

DISCUSSION

In this large, population-based cohort, we have demonstrated that a relatively low proportion (8.7%) of patients will sustain any non-hip fragility fracture in the first year following a hip fracture and that, when restricted to major non-hip fragility fractures, the cumulative 1-year probability after hip fracture was lower still at 2.7%. However, over a 5-year period, the subsequent fracture risk becomes larger with almost one third of patients sustaining a fracture. Secondly, we observed a secular change in subsequent fracture risk, with a 1.4 fold increase in the 1-year risk of subsequent major (non-hip) fragility fracture in the years 2009–2010 when compared to years 2000–2002. The risk of any fracture was 1.8 times higher in 2009–2010 compared with that at the beginning of the decade.

Differences in risk estimates between this and other studies are difficult to evaluate as this is the first study to examine humerus, vertebrae and forearm fractures exclusively after hip fracture. However, when extended to include any (non-hip) fractures, our rates are in line with other studies,[31] one of which found a 1-year cumulative incidence of 7.4 %.[32] Many patients die before they can suffer a subsequent fracture after a hip fracture. Other studies have also concluded that mortality risk dominates fracture risk after hip fracture[33] and that future fractures are dependent upon survival, which in the short term means that older age groups have fewer fractures. The probability of subsequent fracture in this study may have been underestimated for several reasons. One reason could be under-reporting of fractures, in particular, those of the vertebrae, which are often missed or not reported to GPs. This notion is supported by the low number of vertebral fractures (IR 4.12 per 1,000 person years), which is somewhat in contrast to the figure from other studies, usually having a similar IR to forearm and humerus fractures.[5,7] Additionally, a relatively large (9.8%) number of individuals transferred out of the CPRD database, probably to a nursing or care home, where incidence rates of fractures is greater.[34] Finally, due to data recording reasons, this study excluded subsequent hip fractures, which is generally considered to be one of the most important outcomes.

We identified risk factors for subsequent fractures similar to those documented in previous studies.[26] The most important risk factors were female gender, followed by secondary osteoporosis and a history of major fracture, as were estimated both by Cox regression and Fine and Gray regression. However, the estimates of determinants of subsequent fracture that are

strongly influenced by competing mortality risk, such as age, are biased when Cox regression is used as this method fails to take into account competing risk from death. Indeed, Fine and Gray regression analysis showed no differences between age categories and subsequent fracture risk for major (non-hip) fracture and yielded even a lower risk for any (non-hip) fracture for the elderly. A few determinants were not associated with an increased fracture risk. Most notably in this analysis, rheumatoid arthritis was not associated with increased subsequent fracture risk, although it has been generally documented as a well-established risk factor for fracture. The reason for this is unknown as the registration of rheumatoid arthritis within the CPRD is good.[35] Alcohol consumption was also not associated with an increased 1-year risk of subsequent fracture. This is not surprising as only large amounts of alcohol (3 units or more daily) increases the risk of fracture. Finally, falls were not significantly associated with an increased risk of fracture. This is most likely due to under-reporting as falls are not systematically gathered for all elderly CPRD patients.

Comparison of secular trends of subsequent fracture with other studies is difficult as this is the only study that has examined subsequent major (non-hip) and any (non-hip) fragility fracture trends in hip fracture patients. However, Omsland *et al*.,[19] who investigated second hip fractures between 1999 and 2008, found no corresponding decline in second hip fracture. Additionally, a recent report by Smith *et al*.[36] of UK hip fractures hospital admissions has reported a 15.5 % increase in the last decennia, although age- and sex-adjusted rates have remained the same. One explanation for the significant rise in fracture rate could be the corresponding significant fall in mortality found by Klop *et al*.[37] This would further confirm the dependency of fracture risk on mortality at these older ages. Another reason could be the improvement of GP record-keeping. Finally, although there has been a large increase in the prescribing of osteoporotic medication,[38] many studies conclude that prescribing rates are suboptimal with as many as two thirds of patients never receiving any prescription.[39]

The strength of this study is that it is a large, population-based cohort in which longitudinal data are available for risk factors allowing adjustment for drug prescribing, co-morbidities, and lifestyle factors. Additionally, the results in terms of determinants are consistent with those of other studies. This study also has some limitations. Owing to the way records are held within the CPRD, we were unable to include subsequent hip fractures, which account for a substantial proportion (9 %)[3] of subsequent major fragility fractures. Additionally, 15 of the major (non-hip) fragility fractures were recorded as occurring the day after the index hip fracture, and 40 subsequent major (non-hip) fractures occurred within a week. It is quite likely that some of these fractures occurred as part of the initial hip fracture incident. This would cause a small overestimation of subsequent fracture incident rates. The same small overestimation would also apply to the any (non-hip) fracture rates. Furthermore, the generalizability of this study is limited to free-living individuals and excludes those living in nursing and possibly retirement homes. Just under 10 % of the patients transferred out of the database to, most likely, nursing homes where fracture incidence is higher.

In conclusion, the absolute risk of sustaining a major non-hip fragility fracture within 1 year of hip fracture is small. However, secular trends show that there has been a marked increase in the incidence of subsequent fractures. Additionally, the long-term risk of sustaining a subsequent fracture is considerable. Hence, fracture prevention is clearly indicated after hip fracture.

SUPPLEMENTARY TABLE 1 | Comparison of baseline characteristics between hip fracture patients (2000 – 2010) who died or transferred-out of the CPRD within one year of hip fracture and those who completed 1-year follow-up

Characteristic	Patients who completed 1-year follow-up (n=20 952)		Patients who died (n=6576)		Patients who transferred (n= 2988)	
Female, n (%)	16 186	(77.3)	1990	(30.3)	2395	(80.2)
Age (%)						
50-59	1177	(5.6)	122	(1.9)	76	(2.5)
60-69	2461	(11.7)	314	(4.8)	126	(4.2)
70-80	6064	(28.9)	1233	(18.8)	546	(18.3)
80-89	8972	(42.8)	3264	(49.6)	1576	(52.7)
90+	2278	(7.5)	1643	(25.0)	664	(22.2)
BMI category (kg/m^2), n (%)						
< 18	2356	(11.2)	912	(13.9)	381	(12.8)
18 - 25	7023	(33.5)	1808	(27.5)	981	(32.8)
> 25	6795	(32.4)	1529	(23.3)	703	(23.5)
Missing	4778	(22.8)	2327	(35.4)	923	(30.9)
Smoking category, n (%)						
Non-Smoker	10 182	(48.6)	2885	(43.9)	1523	(51.0)
Ex-smoker	3969	(18.9)	1233	(18.8)	509	(17.0)
Current Smoker	4525	(21.6)	1397	(21.2)	568	(19.0)
Missing	2276	(10.9)	1061	(16.1)	388	(13.0)
Alcohol category, n (%)						
No	5043	(24.1)	1592	(24.2)	793	(26.5)
Yes	11 653	(55.6)	3037	(46.2)	1445	(48.4)
Missing	4256	(20.3)	1947	(29.6)	750	(25.1)
Disease history, n (%)						
History of fragility fracture	4096	(19.5)	1201	(18.3)	612	(20.5)
≥ 1 fall (3 – 12 months prior)	1480	(7.1)	727	(11.1)	413	(13.8)
Seconday osteoporosis	1149	(5.5)	454	(6.9)	164	(5.5)
Inflammatory bowel disease	261	(1.2)	76	(1.2)	30	(1.0)
Rheumatoid arthritis	839	(4.0)	189	(2.9)	84	(2.8)
Parkinson's disease	592	(2.8)	288	(4.4)	160	(5.4)
Drug history (in 6 month prior to hip fracture), n (%)						
Antipsychotic	1104	(5.3)	817	(12.4)	323	(10.8)
Antidepressants	4567	(21.8)	1737	(26.4)	841	(28.1)
Anti-epileptics	980	(4.7)	294	(4.5)	120	(4.0)
Corticosteroids (systemic and inhaled)	3546	(16.9)	1289	(19.6)	364	(12.2)
Sedatives and Hypnotics	4237	(20.2)	1435	(21.8)	508	(17.0)
Opioid analgesics	3584	(17.1)	1530	(23.3)	577	(19.3)
Bisphosphonates, strontium ranelate, calcitonin and PTH	2079	(9.9)	581	(8.8)	264	(8.8)
HRT and SERMs	219	(1.0)	32	(0.5)	26	(0.9)
Vitamin D and calcium	3044	(14.5)	965	(14.7)	428	(14.3)

SUPPLEMENTARY TABLE 2 | Incidence rates and Hazard Ratios (95% confidence intervals) for all covariates affecting the 1-year risk of subsequent fracture when taking into account competing mortality risk

	Major (non-hip) Fragility Fracture						Any (non-hip) Fracture					
	No. of fractures	IR [a]	Crude HR [c] (95% CI)		Adjusted HR [d] (95% CI)		No. of fractures	IR [a]	Crude HR [c] (95% CI)		Adjusted HR [d] (95% CI)	
Overall	655	28.19	-		-		2172	70.15	-		-	
Age (years)												
50-59	23	18.57	1.00 (reference)		1.00		115	98.43	1.00 (reference)		1.00	
60-69	49	18.83	0.97	(0.59-1.60)	0.95	(0.58-1.57)	238	96.22	0.96	(0.77-1.20)	0.95	(0.76-1.19)
70-79	208	31.57	1.49	(0.97-2.29)	1.50	(0.97-2.32)	601	95.23	0.88	(0.72-1.07)	0.88	(0.71-1.08)
80-89	303	29.12	1.21	(0.79-1.85)	1.28	(0.83-1.97)	959	95.86	0.79	(0.65-0.96)	0.81	(0.66-0.99)
90+	72	24.72	1.18	(0.53-1.34)	0.92	(0.57-1.49)	259	91.89	0.64	(0.51-0.79)	0.66	(0.52-0.83)
Gender												
Male	89	16.08	1.00 (reference)		1.00		433	81.41	1.00 (reference)		1.00	
Female	566	31.08	2.09	(1.67-2.61)	2.03	(1.61-2.55)	1739	99.62	1.34	(1.21-1.49)	1.32	(1.18-1.47)
Body mass Index (kg/m^2) [b]												
< 18	63	44.97	1.45	(1.11-1.91)	1.38	(1.05-1.81)	161	120.0	1.12	(0.95-1.32)	1.09	(0.92-1.29)
18 - 25	324	27.27	1.00 (reference)		1.00		1105	96.94	1.00 (reference)		1.00	
> 25	268	25.61	0.97	(0.83-1.14)	0.98	(0.83-1.15)	906	90.28	0.96	(0.88-1.05)	0.96	(0.88-1.05)
Smoking Status [b]												
Non-Smoker	343	26.29	1.00 (reference)		1.00		1160	92.64	1.00 (reference)		1.00	
Ex-smoker	136	26.68	1.12	(0.92-1.37)	1.08	(0.89-1.33)	488	100.1	1.11	(1.00-1.24)	1.08	(0.97-1.20)
Current Smoker	176	31.42	1.26	(1.05-1.52)	1.21	(1.00-1.47)	524	97.38	1.03	(0.92-1.14)	1.00	(0.89-1.11)
Alcohol Use [b]												
No	219	26.53	1.00 (reference)		1.00		687	97.80	1.00 (reference)		1.00	
Yes	436	27.46	0.98	(0.83-1.16)	0.96	(0.81-1.13)	1485	94.28	1.02	(0.93-1.11)	1.01	(0.93-1.11)

[a] IR – Incidence Rate (number of events per 1000 patient-years); HR – hazard ratio; 95% CI – 95% confidence interval
[b] Missing values are imputed
[c] Age and sex adjusted
[d] Adjusted for age, sex, body mass index, smoking status, alcohol use, disease history (ever recorded) and drug history (6 months prior)

SUPPLEMENTARY TABLE 3 | Incidence rates and Hazard Ratios (95% confidence intervals) for drug and disease covariates affecting the 1-year risk of subsequent fracture when taking into account competing mortality risk

	Major (non-hip) Fragility Fracture				Any (non-hip) Fracture			
	No. of fractures	IR [a]	Adjusted HR [b] (95% CI)		No. of fractures	IR [a]	Adjusted HR [b] (95% CI)	
Disease History [c]								
History of major fracture	182	39.42	1.47	(1.24-1.76)	525	119.23	1.29	(1.17-1.43)
≥ 1 fall (3-12 months prior)	60	34.39	1.19	(0.96-1.48)	201	116.15	1.11	(0.97-1.26)
Secondary osteoporosis	58	43.60	1.47	(1.12-1.92)	187	148.50	1.42	(1.22-1.65)
Inflammatory bowel disease	8	27.17	0.94	(0.47-1.88)	30	105.88	1.07	(0.75-1.52)
Rheumatoid arthritis	32	34.70	1.13	(0.78-1.63)	90	101.46	1.02	(0.83-1.27)
Parkinson's disease	24	32.33	1.13	(0.75-1.71)	68	95.19	0.93	(0.73-1.19)
Drugs history [c] (in 6 month prior)								
Antipsychotics	40	28.31	0.81	(0.60-1.11)	126	92.37	0.78	(0.66-0.93)
Antidepressants	178	33.44	1.13	(0.95-1.35)	570	112.10	1.15	(1.04-1.26)
Anti-epileptics	39	35.42	1.38	(1.01-1.88)	123	117.54	1.22	(1.02-1.46)
Corticosteroids	71	39.41	1.31	(1.08-1.59)	432	112.28	1.17	(1.05-1.30)
Sedatives and hypnotics	147	35.06	1.04	(0.86-1.25)	441	109.68	1.05	(0.94-1.16)
Opioid analgesics	158	32.69	1.17	(0.99-1.39)	502	108.46	1.07	(0.96-1.17)
Bisphosphonates	85	36.43	0.95	(0.76-1.19)	225	114.41	1.00	(0.88-1.14)
HRT and SERMs	4	16.73	0.54	(0.19-1.46)	20	87.24	0.83	(0.53-1.30)
Vitamin D/Calcium	125	36.45	1.01	(0.83-1.24)	376	114.80	0.97	(0.87-1.08)

[a] IR – Incidence Rate (number of events per 1000 patient-years); HR – hazard ratio; 95% CI – 95% confidence interval
[b] Adjusted for age, sex, body mass index, smoking status, alcohol use, disease history (ever recorded) and drug history (6 months prior)
[c] Reference category is a healthy subject /non user

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CHAPTER 3.2

Mortality in British hip fracture patients, 2000 – 2010: a population-based retrospective cohort study

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ABSTRACT

Background: Data on recent trends in mortality after hip fracture are scarce. Aims were therefore to examine secular trends in all-cause and cause-specific mortality post hip fracture and to compare this to the general population from 2000 to 2010.

Methods: Population-based cohort study within the United Kingdom Clinical Practice Research Datalink and linked to cause of death data for 57.7% of patients. Patients with a first hip fracture (n=31 495) were matched to up to four controls by age, sex, index date, and practice. All subjects were followed for death, and lifestyle, disease and medication history adjusted hazard ratios (HRs) were calculated.

Results: One-year all-cause mortality after hip fracture declined from 2009 and was 14% lower after, compared with before 2009 (22.3% to 20.5%, adj. HR 0.86, 95% CI: 0.81–0.92). The decline was observed for males (≥ 75 years) and females (≥ 85 years). Significant contributors to the decline in mortality post hip fracture were respiratory infections in females as were malignant diseases in males. However, one-year all-cause mortality remained unaltered over the decade when compared to controls with a 3.5-fold and 2.4-fold increased risk in males and females respectively. No significant changes were observed in the relative risks for one-year cause-specific mortality for both genders.

Conclusions: One-year mortality after hip fracture has declined over the last decade in the UK. However, the difference in one-year mortality between hip fracture patients and the general population remained unaltered. These observations highlight the need for the continued implementation of evidence-based standards for good hip fracture care.

INTRODUCTION

Hip fractures are a major public health concern in terms of morbidity, healthcare costs and mortality. A large meta-analysis showed that mortality in the year post hip fracture ranges from 20% to 26% among elderly females and males respectively. When compared to patients without hip fracture, mortality is 2 -to 4-fold higher in the subsequent year, and is higher for men than for women at any given age. This excess mortality persists even for ten years following the fracture.[1] Although there is little change in age-standardised hip fracture rates in the United Kingdom, the absolute number of hip fractures will continue to rise due to the ageing of the population.[2]

Despite the advances in the surgical and medical management of hip fractures data on recent trends in mortality are scarce. Secular trends for mortality after hip fracture have been reported from 1968 through 1998 in the United Kingdom. Between 1968-73 and 1979-83 there was a significant decline in one-year mortality and this stabilised in the period thereafter.[3] A US study that used 20% of all Medicare claims found no reduction in one-year mortality from 1995 to 2005.[4] Conversely, a study in Texas reported a significant decrease in hip fracture-related mortality by 0.8% per year between 1990 – 2007 in males but not in females.[5]

However, it remains unknown whether the difference in mortality between hip fracture patients and the general population has changed over the last decade. In addition, cause-specific trends for mortality after hip fracture remain to be determined. Therefore, the aims of this study were (1) to describe all-cause and cause-specific one-year mortality following a hip fracture between the years 2000 and 2010 and (2) to determine, over the last decade, the relative difference in (all-cause and cause-specific) mortality between individuals with a hip fracture and controls.

METHODS

STUDY POPULATION

A cohort study was conducted within the Clinical Practice Research Datalink (CPRD) (formerly known as the General Practitioner Research Database, www.cprd.com). This database contains computerised medical records of 625 primary care practices in the United Kingdom, representing 8% of the total population. Data recorded in the CPRD includes demographic information, laboratory tests, specialist referrals, hospital admissions, prescription details, and lifestyle variables such as body mass index (BMI), smoking status, and alcohol consumption. Previous studies have shown a high validity of hip fracture registration (>90% of fractures were confirmed)[6], and high degrees of accuracy and completeness of these data have been shown for other diagnoses.[7-9] In addition, a high level of sensitivity (98%) and specificity (99%)

for mortality recording has been observed.[10] Linkage of CPRD data to the Office for National Statistics (ONS) was possible for 57.7% of the population captured within the CPRD, who are all residing in England and Wales. The ONS provides data for the cause(s) of death and the exact date of death as recorded on death certificates by a registered medical practitioner who has attended the patient during their last period. Death certificates are divided into part I (the primary cause of death) and part II (conditions that may have contributed significantly to the death). The all-cause mortality analysis was performed from January 1st 2000 up to December 31st 2011 with unlinked CPRD data. For analyses concerning cause-specific mortality, CPRD data was linked to death registration data (ONS) from January 1st 2001 up to December 31st 2011.

The study population consisted of all patients aged ≥ 18 years with a CPRD read code for their first hip fracture between January 1st 2000 and December 31st 2010. The index date was defined as the first record for hip fracture. Patients with a read code for unspecified fractures or unspecified femoral fractures before the index date were excluded, since it was uncertain if the index fracture was actually the first hip fracture of the patient.

SELECTION OF CONTROLS

To determine (changes in) relative one-year mortality we matched each hip fracture patient to up to four control patients without a read code for a hip fracture by age, sex, calendar time (index date), and practice using the incidence density sampling technique.

OUTCOMES

The primary outcome of interest was one-year all-cause mortality. All patients were followed from the index date to either the end of the study period (up to 365 days after the index date), the date of transfer of the patient out of the practice area, or the patient's death as recorded in the CPRD database, whichever came first. The secondary outcome was one-year cause-specific mortality (using all entries recorded on the death certificates) and was assessed in the population eligible for linkage between CPRD and ONS data. Patients were censored at the end of the study period if it occurred before the date of death. Specific causes of death were grouped into the following categories using the International Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10): cardiovascular disease (ICD-10: I0-I5, I7-I9), cerebrovascular disease (ICD-10: I6), respiratory infections (ICD-10: J0-J2), non-respiratory infections (ICD-10: A0-B9, N39.0), malignant neoplasms (ICD-10: C), non-infectious respiratory diseases (ICD-10: J3-J9), injuries (ICD-10: S, T0-T14), dementia (ICD-10: F00-F03, G30), and all other causes of death.

DEFINITION OF COVARIATES

General risk factors/possible confounders (according to the presence of CPRD read codes) for mortality that were considered for analyses were age, sex, smoking status (a record of

currently smoking, ex-smoking, non-smoking), alcohol use (yes, no), the most recent record of the body mass index (BMI) before the index date (< 20, 20 – 25, > 25 kg/m^2), a history of chronic diseases (ischemic heart disease, cerebrovascular disease, heart failure, chronic kidney disease, chronic obstructive pulmonary airway disease [COPD], dementia), major infections (sepsis, meningitis), major osteoporotic fracture (radius/ulna, humerus, clinical vertebrae), malignant neoplasms, and secondary osteoporosis. A record for pneumonia was assessed within six months before the index date.[4,11] Furthermore, a prescription record for anti-diabetic drugs and for psychotropic drugs, glucocorticoids and bisphosphonates in the six months before the index date were considered since these drugs are associated with falls and fractures and may therefore influence mortality risk.[12-16] Besides age, all covariates were handled as categorical variables in the analyses.

STATISTICAL ANALYSES

Hazard Ratios [HRs] for one-year all-cause and cause-specific mortality were estimated by Cox proportional hazards regression (SAS 9.2 PHREG procedure). One-year all-cause mortality following hip fracture was compared between calendar years of the total study period (according to the year of first hip fracture [index date]) using the year 2000 as a referent group). Based on these results, cut-off points were defined to compare the one-year all-cause and cause-specific mortality risks between year periods, stratified by sex. The HRs were adjusted for significant determinants for one-year mortality after hip fracture, which were defined by stepwise backward elimination with a significance level of 0.05. Kaplan-Meier plots were used to visualize the age- and gender- specific cumulative incidence rates for one-year all-cause mortality over time, and were stratified by year periods (log-rank test for comparison).

Furthermore, we estimated HRs for the relative differences in one-year mortality between hip fracture patients and control subjects. HRs for relative one-year all-cause and cause-specific mortality were estimated for each year period, and were compared by including an interaction term into the model (calendar year cut-off point * indicator variable for hip fracture). HRs were adjusted for all covariates that changed the beta-coefficient of hip fracture with ≥ 1% in an age-adjusted analysis.

Since for some of the covariates (BMI, smoking status and alcohol use) missing data were present multiple imputation was used. Data were imputed five times using the automatic multiple imputation method in SPSS version 19.0. All analyses were performed separately for the five imputed datasets and HRs were pooled using the MIANALYZE procedure in SAS 9.2.

In sensitivity analyses changes in one-year all-cause mortality in hip fracture patients and relative to control subjects were estimated after restriction of the study population to those eligible for linkage of CPRD data to the Office for National Statistics, and after restriction to a population without missing data for life-style factors (complete-case analysis).

RESULTS

A total of 31,495 patients with a first hip fracture and 116,649 control subjects were included (Table 1). Most hip fractures occurred in women (74.7%) at a higher mean age than in men (80.5 ± 10.5 versus 74.1 ± 14.8). During the total study period one-year mortality was 22.0% post hip fracture and 7.8% in control subjects without hip fracture.

TABLE 1 | Baseline characteristics of hip fracture patients and controls

	Males		Females	
	Hip fracture	Controls	Hip fracture	Controls
Characteristic	7979	30,037	23,516	86,612
Follow-up (days, mean ± SD)	282 ± 130	345 ± 67	292 ± 124	339 ± 76
Age (mean ± SD)	74.1 ± 14.8	73.3 ± 14.8	80.5 ± 10.5	79.7 ± 10.5
Age categories (%)				
< 75 years	38.4	40.5	21.7	23.3
75 – 84 years	36.7	38.1	38.5	40.3
≥ 85 years	24.9	21.5	39.9	36.5
BMI categories (kg/m^2) (%)				
< 20	8.9	3.4	13.1	7.1
20 - 25	33.8	29.2	31.6	29.0
> 25	34.2	47.9	27.8	40.4
Missing [a]	23.1	19.5	27.5	23.5
Alcohol use (%)				
Yes	63.6	68.7	49.7	53.6
No	16.9	13.4	26.4	25.2
Missing [a]	19.5	17.9	23.9	21.2
Smoking (%)				
Current	28.1	21.8	19.9	16.5
Ex-smoker	27.6	30.8	15.2	16.1
Non-smoker	33.9	37.8	52.1	56.1
Missing [a]	10.4	9.6	12.9	11.2
Co-morbidities (ever before index date unless otherwise specified, %)				
Chronic kidney disease	11.5	9.3	10.8	10.2
Cerebrovascular diseases	20.5	11.9	16.7	12.3
Heart failure	10.3	6.8	8.7	7.8
Ischemic heart disease	22.5	22.2	17.7	17.2
Meningitis	0.3	0.2	0.2	0.2
Pneumonia (within 6 months before)	7.3	4.8	6.4	5.4
Sepsis	0.5	0.2	0.3	0.2
Major osteoporotic fracture	8.9	3.8	14.4	8.5
Dementia	8.7	2.5	12.5	5.7
COPD	12.9	8.2	7.7	5.6
Malignant neoplasms	17.2	14.0	14.1	12.5
Malignant neoplasm bone	0.1	0.0	0.0	0.0
Secondary osteoporosis [b]	7.5	3.5	5.4	3.4

Medication use (within 6 months before index date, %)				
Benzodiazepines	10.0	4.8	15.7	10.8
Antipsychotic drugs	5.9	1.5	7.7	3.4
Antidepressants	18.4	8.1	24.9	15.4
Anti-convulsants	5.8	1.9	4.2	2.2
Glucocorticoids	7.3	4.9	7.9	6.0
Bisphosphonates	3.8	1.9	11.4	7.8
Oral anti-diabetics	6.9	6.8	5.9	5.4

Abbreviations: SD; standard deviation, BMI; body mass index, COPD; chronic obstructive pulmonary disease.
[a] Missing data were imputed five times and imputed datasets were used for analyses.
[b] Type I diabetes mellitus, osteogenesis imperfecta, osteomalacia, hypogonadism, premature menopause, malnutrition, [gastrointestinal tract] mal-absorption, coeliac disease, anorexia, and liver diseases including chronic liver disease, hepatitis, cirrhosis, neoplasms of the liver.

TRENDS FOR ONE-YEAR MORTALITY AFTER HIP FRACTURE

The trend for one-year mortality from all causes after hip fracture, adjusted for statistically significant determinants for mortality, is shown for each calendar year in Figure 1. When compared to the year 2000, one-year mortality remained stable until 2008 and was significantly decreased from 2009 onwards (2000 – 2008 vs. 2009 – 2010: 22.3% to 20.5%, adjusted [adj.] Hazard Ratio [HR] 0.86, 95% CI: 0.81 – 0.92). The decline was greater for males (26.9% to 22.8%, adj. HR 0.79, 95% CI: 0.71 – 0.89) than for females (20.8% to 19.5%, adj. HR 0.90, 95% CI: 0.83 – 0.98). Similar trends for one-year all-cause mortality were observed in sensitivity analyses where the study population was restricted to those eligible for linkage of CPRD data to ONS data (adj. HR 0.88, 95% CI: 0.81 – 0.96) and upon restriction to the population without missing data for life-style factors (adj. HR 0.89, 95% CI: 0.82 – 0.96).

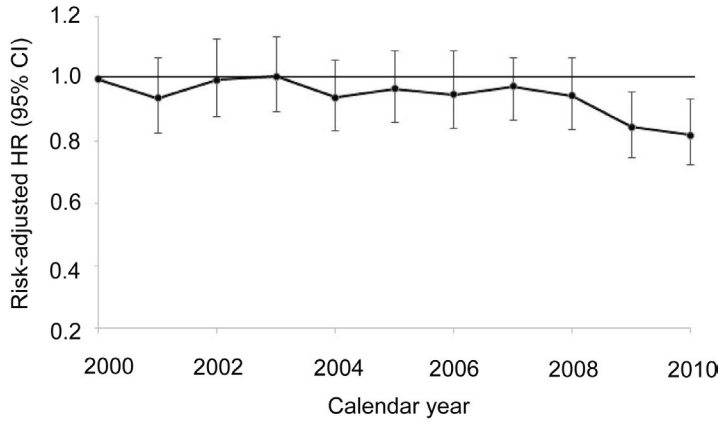

FIGURE 1 | Risk-adjusted HRs for one-year all-cause mortality from 2001 – 2010, as compared to 2000. Abbreviations: HR; hazard ratio, CI; confidence interval. Hazard ratios were adjusted for age, sex, use of benzodiazepines, antipsychotic drugs, antidepressants, anti-convulsants, glucocorticoids in the six months before, a history of cerebrovascular disease, heart failure, ischemic heart disease, dementia, COPD, malignant neoplasms, fracture (clinical vertebrae, humerus, radius/ulna), secondary osteoporosis, pneumonia (≤6 months before),body mass index, alcohol use, and smoking status.

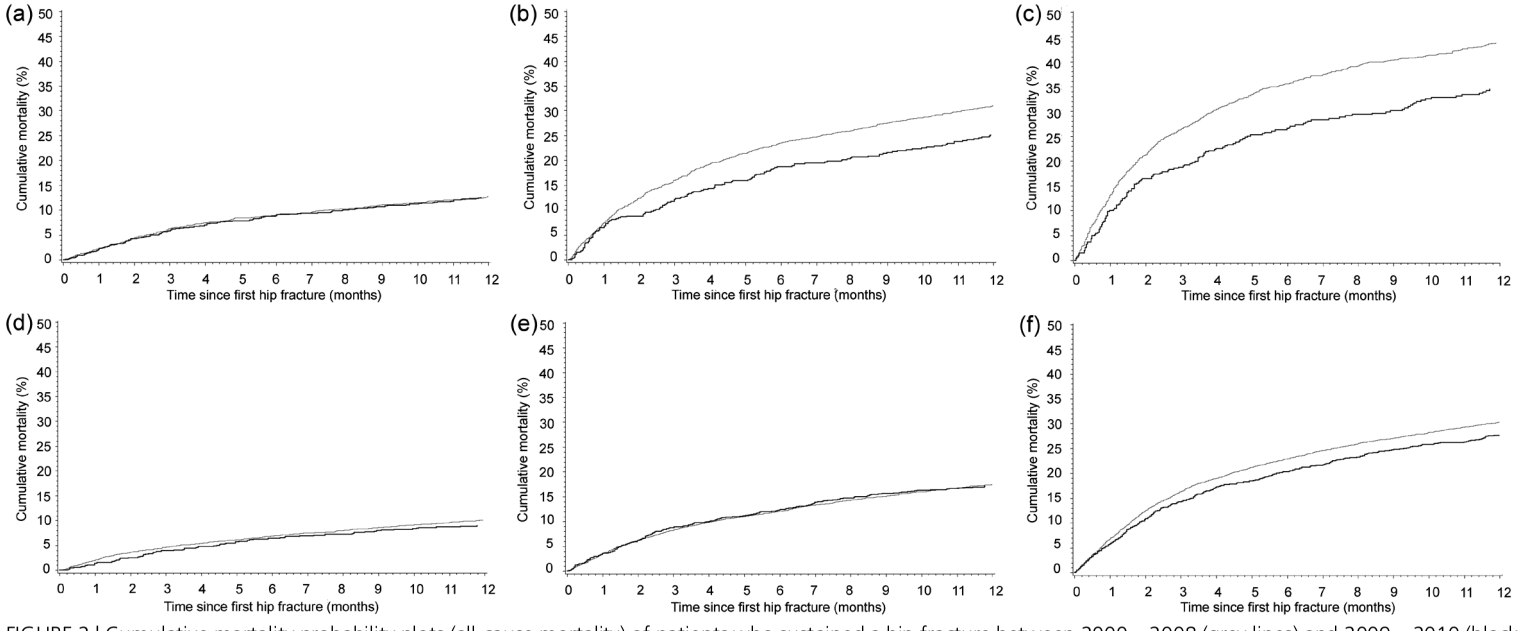

FIGURE 2 | Cumulative mortality probability plots (all-cause mortality) of patients who sustained a hip fracture between 2000 – 2008 (grey lines) and 2009 – 2010 (black lines), stratified by sex and age categories. Plot a, b, c represent male patients (a: < 75 years, b: 75 – 84 years, c: ≥ 85 years). Plot d, e, f represent female patients (d: < 75 years, e: 75 – 84 years, f: ≥ 85 years).

Figure 2 shows that the decline in one-year all-cause mortality after hip fracture was attributable to males aged 75 – 84 years (31.1% to 25.1%, log-rank p-value <0.0001) and ≥ 85 years (43.8% to 34.4%, log-rank p-value <0.0001), but not to males younger than 75 years (12.8% to 12.9%, log-rank p-value 0.84). For females, a significant decline from 2009 onwards was only observed for the oldest age group of ≥ 85 years (30.4% to 27.7%, log-rank p-value <0.0001).

Trends and incidence rates for one-year cause-specific mortality after hip fracture were different for males and females (Table 2). One-year mortality from malignant neoplasms was significantly (30%) lower in males who sustained a hip fracture in 2009 – 2010 as compared to 2001 – 2008. In females, there was a significant decrease in one-year mortality caused by respiratory infections. We did not observe significant changes for one-year mortality from other causes for males and females who sustained a hip fracture.

TABLE 2 | One-year cause-specific mortality after hip fracture, stratified by sex

Cause of death [a]	Incidence rate [b]		Adj. HR (95% CI) [c]	
	2001 – 2008	2009 – 2010	2001 – 2008 (reference category)	2009 – 2010
Males				
Cardiovascular diseases	138.1	126.4	1.00	0.92 (0.73 – 1.15)
Cerebrovascular diseases	43.6	33.7	1.00	0.78 (0.51 – 1.18)
Respiratory infections	112.7	98.7	1.00	0.88 (0.69 – 1.13)
Malignant neoplasms	85.7	61.4	1.00	0.70 (0.51 – 0.95)
Non-respiratory infections	28.5	28.9	1.00	0.97 (0.60 – 1.55)
Respiratory diseases (non-infectious)	73.6	85.4	1.00	1.19 (0.90 – 1.57)
Injuries	66.8	57.8	1.00	0.84 (0.60 – 1.16)
Dementia	44.4	66.2	1.00	1.34 (0.96 – 1.88)
None of the above	186.7	175.7	1.00	0.90 (0.75 – 1.09)
Females				
Cardiovascular diseases	90.9	90.5	1.00	0.98 (0.83 – 1.16)
Cerebrovascular diseases	38.7	35.6	1.00	0.90 (0.69 – 1.17)
Respiratory infections	76.4	56.0	1.00	0.72 (0.59 – 0.89)
Malignant neoplasms	40.6	37.1	1.00	0.87 (0.67 – 1.13)
Non-respiratory infections	22.1	24.6	1.00	1.08 (0.78 – 1.49)
Respiratory diseases (non-infectious)	39.0	44.4	1.00	1.06 (0.83 – 1.35)
Injuries	52.4	61.2	1.00	1.17 (0.95 – 1.44)
Dementia	48.9	60.7	1.00	1.13 (0.92 – 1.40)
None of the above	147.8	145.4	1.00	0.97 (0.85 – 1.11)

Abbreviations: adj.; adjusted, HR; Hazard Ratio, CI; Confidence Interval.
[a] Causes of death are not mutually exclusive (primary causes, as well as causes that may significantly have contributed to death were taken into account)
[b] Number of cause-specific deaths per 1,000 patient-years.
[c] Adjusted for age, use of benzodiazepines, antipsychotic drugs, antidepressants, anti-convulsants, glucocorticoids in the six months before, a history of cerebrovascular disease, heart failure, ischemic heart disease, dementia, COPD, malignant neoplasms, fracture (spine, humerus, radius/ulna), secondary osteoporosis, pneumonia (≤ 6 months before), body mass index, alcohol use, and smoking status.

TRENDS FOR RELATIVE DIFFERENCES IN ONE-YEAR MORTALITY

During the total study period, the hazard for one-year all-cause mortality was 3.5 times (95% CI: 3.28 – 3.74) greater for male hip fracture patients than control subjects after adjustment for age, co-morbidities, medication use and lifestyle factors. This risk was 2.4-fold (95% CI: 2.31 – 2.50) greater than controls for females. Table 3 shows the trend for relative differences in one-year all-cause mortality (hip fracture patients as compared to control subjects). Relative one-year mortality was not significantly altered in 2009 – 2010 as compared to 2000 – 2008 (adj. HR 1.08, 95% CI: 0.99 – 1.18). The unchanged relative one-year all-cause mortality was also observed upon stratification by sex (males: adj. HR 0.98, 95% CI: 0.84 – 1.16, females: adj. HR 1.08, 95% CI: 0.98 – 1.21) and age categories (< 75 years: adj. HR 1.18, 95% CI: 0.86 – 1.61, 75 – 84 years: adj. HR 1.15; 95% CI: 0.99 – 1.35, ≥ 85 years: adj. HR 1.03, 95% CI: 0.92 – 1.16). In sensitivity analyses we observed similar trends for relative one-year all-cause mortality when the study population was restricted to those eligible for linkage of CPRD data to ONS data (2009 – 2010 vs. 2000 – 2008: adj. HR 1.04, 95% CI: 0.93 – 1.16) and after restriction to a study population without missing data for life style factors (adj. HR 1.09, 95% CI: 0.98 – 1.21).

TABLE 3 | One-year all-cause mortality after hip fracture as compared to control subjects, stratified by age and sex

	Adjusted HR (95% CI)	
	2000 – 2008	2009 – 2010
Control subjects	1.00 (reference category)	1.00 (reference category)
Hip fracture patients [a]	2.63 (2.54 – 2.72)	2.80 (2.58 – 3.04)
By sex [b]		
Males	3.60 (3.35 – 3.87)	3.41 (2.94 – 3.95)
Females	2.39 (2.29 – 2.49)	2.55 (2.31 – 2.82)
By age categories [c]		
< 75 years	4.80 (4.20 – 5.47)	6.21 (4.55 – 8.48)
75 – 84 years	2.80 (2.63 – 2.97)	3.05 (2.63 – 3.54)
≥ 85 years	2.29 (2.19 – 2.41)	2.32 (2.08 – 2.59)

Abbreviations: HR; hazard ratio, CI; confidence interval(a) Adjusted for age, sex, use of benzodiazepines, antipsychotic drugs, antidepressants, anti-convulsants, glucocorticoids in the six months before, a history of cerebrovascular disease, heart failure, dementia, COPD, malignant neoplasms, secondary osteoporosis, pneumonia (≤ 6 months before), body mass index, alcohol use, and smoking status.
(b) Adjusted for (a) with the exception of sex.
(c) Adjusted for (a) with the exception of age.

Relative one-year mortality remained unaltered over the study period for all specific causes of death in both males and females (Table 4). However, although not significant, there was a trend towards a lower relative risk for one-year mortality from respiratory infections in females who had sustained a hip fracture in 2009 – 2010 as compared to 2000 – 2008 (adj. HR 0.77, 95% CI: 0.59 – 1.01). In addition, the relative risk for one-year mortality caused by malignant neoplasms tended to be lower for males who had sustained a hip fracture in 2009 – 2010 as compared to 2000 – 2008 (adj. HR 0.68, 95% CI: 0.46 – 1.00).

TABLE 4 | One-year cause-specific mortality after hip fracture as compared to control subjects, stratified by sex

	Adjusted HR (95% CI) [a]	
	2001 – 2008	2009 – 2010
Control subjects	1.00 (reference category)	1.00 (reference category)
Male hip fracture patients		
Cardiovascular diseases	3.38 (2.91 – 3.92)	3.75 (2.83 – 4.97)
Cerebrovascular diseases	2.78 (2.13 – 3.62)	2.15 (1.30 – 3.57)
Respiratory infections	4.32 (3.60 – 5.18)	4.81 (3.38 – 6.85)
Malignant neoplasms	3.21 (2.66 – 3.87)	2.21 (1.55 – 3.16)
Non-respiratory infections	5.12 (3.55 – 7.38)	5.63 (2.85 – 11.12)
Respiratory diseases (non-infectious)	3.71 (2.98 – 4.62)	5.54 (3.74 – 8.20)
Injuries	27.86 (17.44 – 44.53)	30.00 (11.79 – 76.38)
Dementia	3.63 (2.69 – 4.89)	3.95 (2.52 – 6.18)
None of the above	5.37 (4.63 – 6.22)	5.72 (4.35 – 7.51)
Female hip fracture patients		
Cardiovascular diseases	2.29 (2.09 – 2.50)	2.51 (2.05 – 3.07)
Cerebrovascular diseases	1.97 (1.72 – 2.26)	2.11 (1.55 – 2.89)
Respiratory infections	2.87 (2.58 – 3.19)	2.21 (1.71 – 2.86)
Malignant neoplasms	2.16 (1.89 – 2.47)	1.91 (1.41 – 2.57)
Non-respiratory infections	2.89 (2.39 – 3.51)	2.21 (1.51 – 3.24)
Respiratory diseases (non-infectious)	2.66 (2.30 – 3.07)	2.92 (2.15 – 3.97)
Injuries	20.94 (16.37 – 26.79)	25.00 (14.74 – 42.42)
Dementia	2.60 (2.27 – 2.98)	2.65 (2.04 – 3.45)
None of the above	3.45 (3.19 – 3.73)	3.26 (2.74 – 3.86)

Abbreviations: HR ; hazard ratio, CI; confidence interval
[a] Adjusted for age, use of benzodiazepines, antipsychotic drugs, antidepressants, anti-convulsants, glucocorticoids in the six months before, a history of cerebrovascular disease, heart failure, dementia, COPD, malignant neoplasms, secondary osteoporosis, pneumonia (≤ 6 months before), body mass index, alcohol use, and smoking status.

DISCUSSION

This study shows that one-year all-cause mortality has declined over recent years for both sexes amongst British hip fracture patients, a trend which was more pronounced for males. The significant contributors to the decline in all-cause mortality were a decrease in mortality from respiratory infections in females and from malignant neoplasms in males. However, the one-year mortality risk from all causes remained unaltered when compared to control subjects with a 3.5-fold and 2.4-fold elevated risk in males and females respectively. Furthermore, the risks for one-year cause-specific mortality for both genders did not change significantly compared to controls.

The stable one-year mortality post hip fracture from 2000–2008 is consistent with unchanged age- or risk-adjusted one-year mortality observed in Hong Kong (2001–2009),[17] Southern Australia (2002–2008),[18] Finland (2000–2007),[19] and in the USA (1995–2005).[4] However, an English study that included 574,482 hip fracture patients showed a decrease in in-hospital mortality between 1998 and 2009 of 19.0% in women and of 29.3% in men.[2] In fact, case fatality rates continued to increase from 1998 until 2005 and were substantially decreased from 2007/2008 in both sexes. The timing of the decrease was similar to that observed in our study, as was the larger decline in mortality for males as compared with females.

To the best of our knowledge, this is the first study that has showed, over the past decade, secular mortality trends post hip fracture which were compared to survival trends in the general population. The unchanged difference in one-year all-cause mortality between hip fracture patients and control subjects indicates a decline in mortality for the general population of the United Kingdom. This is supported with death registration data of the entire population of England and Wales; age-standardised mortality decreased with 15.1% between 2000–2008 and 2009–2010.[20] The unchanged relative risk for one-year mortality therefore suggests that the decline in mortality amongst hip fracture patients is the result of general advances in health and the health care system, but that hip-fracture related mortality has not decreased significantly.

The increased risk of death after hip fracture for all specific causes reflects the multi-morbidity and frailty of this patient group, which at least in part may be inevitably responsible for the increased death rate compared to the general population. However, it should be elaborated more which specific causes of death are actually preventable in order to reduce the excess mortality. Respiratory infections are well-established complications arising from hip fracture. Their occurrence may be ameliorated by a shorter time to operation, shorter hospital stay and quicker mobilisation.[21] Since 2007 the National Hip Fracture Database (NHFD) was launched jointly by the British Orthopaedic Association (BOA) and the British Geriatrics Society (BGS). This UK-wide system allows auditing of hospitals against evidence-based standards that promote faster time to operation, multidisciplinary rehabilitation services and secondary prevention of (hip) fractures.[22] In addition, the Best Practice Tariff incentivises the achievement of the care standards from 2010 onwards.[23] Although not significant, there was a decline in the relative risk for mortality from respiratory infections amongst female hip fracture patients. If this decline was related to the introduction of the care standards, it remains elusive why this was not observed for males. However, it should be noted that there was limited power to detect small changes in cause-specific mortality.

This study has several strengths. We have presented mortality outcomes in a large representative sample of hip fracture patients and controls. Our results are consistent with previous studies related to hip fracture in general in terms of proportion of men and women, mean age and

consistently higher mortality in males as compared to females.[17, 24] The observed hazard ratio for relative one-year mortality was similar to that documented in a large meta-analysis which reported a one-year relative hazard of 3.7 (95% CI: 3.3–4.1) in males and of 2.9 (95% CI: 2.5–3.3) in females.[1] In addition, our data source had detailed longitudinal information on risk factors for mortality including co-morbidities, drug prescribing and lifestyle factors (e.g. body mass index). Therefore we were able to adjust one-year mortality for these factors. Furthermore, by linkage to death certificates for a subset of the study population we were able to present changes in cause-specific mortality. The reported determinants for one-year mortality and the causes of death are in line with those previously reported by others.[4, 11, 14-16, 25-29]

There are also various limitations to this study. Although we have adjusted one-year mortality for numerous confounding factors, residual confounding may still have been present. Propensity score adjustment or matching are alternative methods to address this concern but they were not included in this study. A large Medicare study, however, indirectly showed very similar results for one-year mortality after hip fracture as compared to control subjects when high-dimensional propensity score matching was used.[30] They found an incidence proportion ratio of 2.65 (95% CI: 2.56–2.75) for one-year all-cause mortality in community-dwelling patients, as compared to a relative risk of 2.65 (95% CI: 2.57–2.74) in the present study. In addition, changes in all-cause mortality in hip fracture patients and relative to controls were based on mortality registration in the CPRD. Mortality outcomes of patients who moved to a nursing home after their hip fracture were not recorded. A change in the discharge destination over time could therefore have biased observed trends in mortality risk. However, linkage of the CPRD to the ONS, which does include mortality outcomes of patients who moved to a nursing home, provided a similar trend for mortality. Furthermore, this study includes only community-dwelling patients at the time of hip fracture and generalization of results may not be applicable to patients who sustained a hip fracture in a nursing home, who are likely to have a higher mortality risk.[31] Another limitation was the presence of missing data for life style factors. We dealt with this problem by multiple imputation, the validity of which has been demonstrated previously;[32, 33] similar results were observed with five separate imputations and in the complete case analysis.

In conclusion, we have found a secular decrease in one-year mortality post hip fracture over the last decade in the UK population. This decline was attributable to mortality trends in the oldest age groups; the underlying causes for the observed decline differed between males and females. Despite the reassuring secular decrease in one-year mortality across both hip fracture patients and controls, one-year mortality after hip fracture thus remains substantially elevated when compared to controls. This finding reinforces the need for continued development of multidisciplinary care pathways and universal implementation of best practice in the care of these vulnerable patients.

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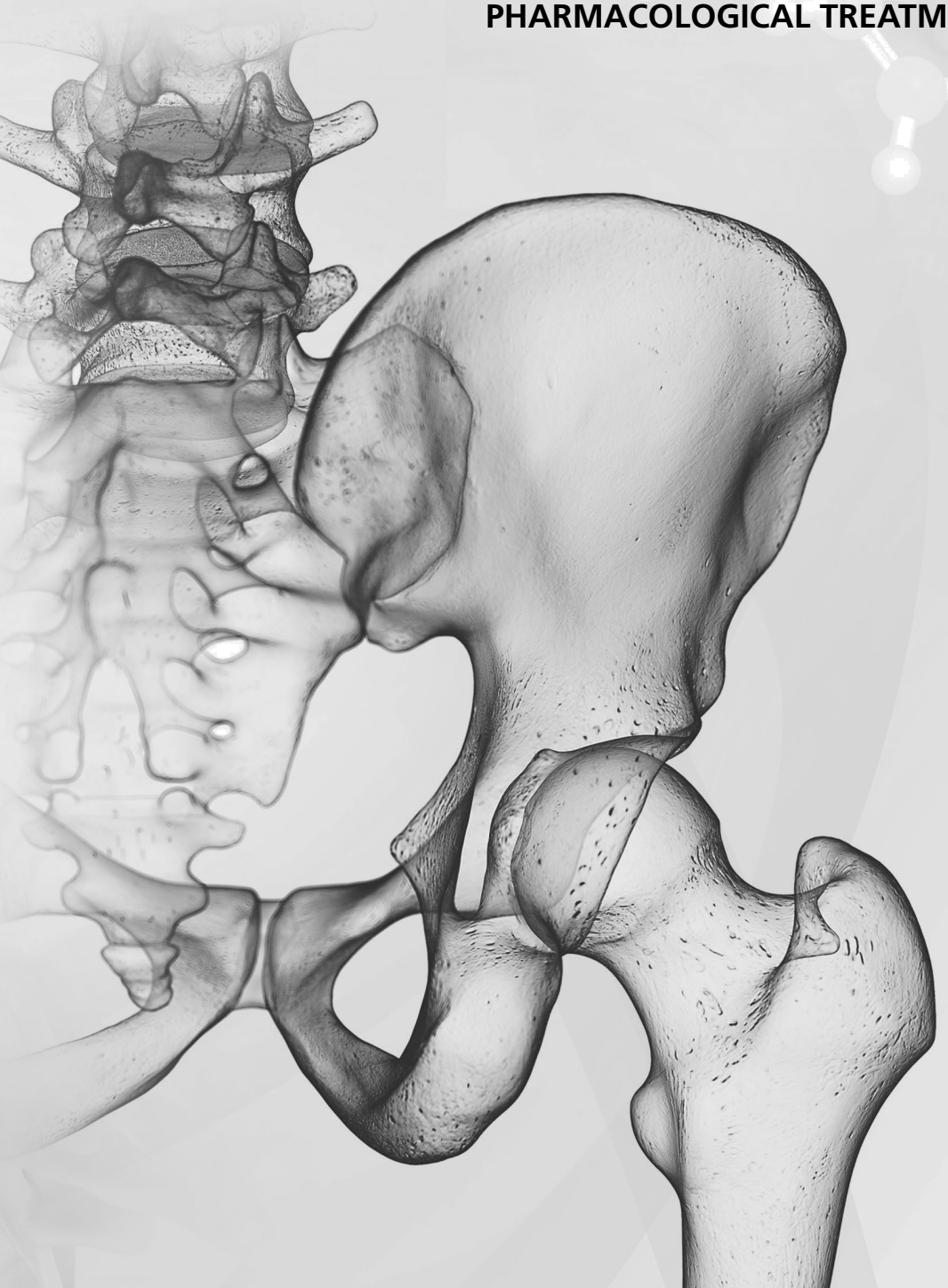
CHAPTER 4

PHARMACOLOGICAL TREATMENT



CHAPTER 4.1

Anti-osteoporosis drug prescribing after hip fracture in the UK: 2000 – 2010

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ABSTRACT

Summary: The probability of initiating with anti-osteoporosis therapy increased from 7% in 2000 to 46% in 2010. This improvement was greater for patients over the age of 75 years. Men, those overweight, having dementia or exposed to antipsychotics, sedatives/hypnotics or opioid analgesics were significantly less likely to receive anti-osteoporosis drugs.

Introduction: The objective of this study was to examine trends and determinants of anti-osteoporosis drug prescribing after hip fracture in the UK between 2000 and 2010.

Methods: Data were extracted from the UK Clinical Practice Research Datalink for patients ≥ 50 years who had a first hip fracture between 2000 and 2010 and who did not currently (≤ 6 months prior) receive anti-osteoporosis drugs (bisphosphonates, strontium ranelate, parathyroid hormone, calcitonin and raloxifene) (n = 27 542). The cumulative incidence probability of being prescribed anti-osteoporosis drugs within 1 year after hip fracture was estimated by Kaplan-Meier life-table analyses. Determinants for treatment initiation were estimated by Cox proportional hazards models.

Results: The probability of being prescribed any anti-osteoporosis drug after hip fracture increased from 7% in 2000 to 46% in 2010. This trend was more marked in patients ≥ 75 years. The increase in prescribing of anti-osteoporosis drugs was complemented by a similar increase in vitamin D/calcium provision. Cumulative incidence of receiving anti-osteoporosis therapy was greater at any given point in time in women (8% in 2000, 51% in 2010) compared to men (4% in 2000, 34% in 2010). In addition to male gender, multivariable Cox regression identified reduced likelihood of receiving anti-osteoporosis drugs for those being overweight, having dementia and exposed to psychotropic drugs (antipsychotics, sedatives/hypnotics) or opioid analgesics.

Conclusion: Although the prescribing of anti-osteoporosis drugs after hip fracture has increased substantially since 2000, the overall rate remained inadequate, particularly in men. With the continuing increase in the absolute number of hip fractures, further research should be made into the barriers to optimize osteoporosis management.

INTRODUCTION

Osteoporosis is a growing public health issue affecting an estimated 2.8 million people within the UK.[1] Osteoporosis results in fragility fractures, the most serious of which are hip fractures. In the last decade, absolute numbers of hospital admissions for hip fractures have increased by 15.5%, despite age- and sex-standardised rates remaining stable since 2003.[2] A history of hip fracture increases the risk of future fracture 3.2 times when compared to patients without a hip fracture,[3] and this risk is greatest in the first year and remains elevated for at least 5 years.[4,5]

Hence, post-fracture treatment with anti-osteoporosis drugs is important to prevent the occurrence of new fragility fractures. Over the decade 2000–2010, the therapies available for treatment of osteoporosis have changed markedly. Initially, hormone replacement therapy (HRT) was the first-line osteoporosis treatment.[6] However, since the Woman's Health Initiative trial in 2002 demonstrated that the risk of coronary heart disease, pulmonary embolism, stroke and breast cancer was greater than the benefits conferred by this therapy, its use has been limited to the short-term relief of menopausal symptoms.[7] Since then, bisphosphonates have been the mainstay of treatment for osteoporosis. Bisphosphonates have been shown to reduce the risk of hip fractures by 30–50% and vertebral fractures by 30–70%.[8] From 2005 onwards, the National Institute for Health and Clinical Excellence (NICE) has also endorsed the use of raloxifene, teriparatide, strontium ranelate and calcitonin (although now withdrawn) for secondary fracture prevention. Despite these readily available effective treatments, a care gap in pharmacological prevention of subsequent fractures has been documented worldwide.[9-11]

Given the ageing population and therefore the increasing number of hip fractures, it is important to know the trend in prescribing practice for anti-osteoporosis drugs and to identify patients at risk of not receiving these drugs. Fortunately, several but not all, studies have shown an improvement in anti-osteoporosis drug prescribing between the late 1990s and the first half of the twenty-first century, where few studies have investigated prescribing practices over more recent years[12-20] or have concerned concomitant prescribing of anti-osteoporosis drugs with vitamin D and/or calcium supplements.[21-23] The latter is important since clinical trials demonstrating efficacy of anti-osteoporosis drugs were all conducted among participants receiving adequate levels of calcium and vitamin D. In 2010, a national clinical audit in the UK showed that as many as 40% of all hip fracture patients did not receive any form of anti-osteoporosis drug treatment within 12 weeks.[24] Numbers for concomitant or solely prescribing of anti-osteoporosis drugs and calcium/vitamin D were not provided, and prescribing practices were not presented beyond age and gender while other patient characteristics may influence prescribing practice as well. Individual data linking drug prescribing and patient characteristics (e.g. previous fractures, lifestyle variables, co-morbidities, poly-pharmacy) would greatly assist in determining which patient groups are at increased risk of not receiving anti-osteoporosis drug treatment after hip fracture.

Therefore, the objective of the present study was to investigate the trends in prescribing of anti-osteoporosis drugs and co-prescribing with vitamin D/calcium supplements in hip fracture patients, who were not currently in receipt of anti-osteoporosis drugs, within a primary care setting in the UK between 2000 and 2010. Additionally, we aimed to examine which patient characteristics influenced the initialization of anti-osteoporosis drug treatment.

METHODS

SOURCE POPULATION

The population was sourced from the Clinical Practice Research Datalink (CPRD) which contains anonymized electronic health records from 625 primary care practices from across the UK representing around 8% of the population. The records include details of all diagnoses and prescriptions issued by NHS general practitioners, specialist referrals, hospital admissions and lifestyle variables (e.g. body mass index, smoking status) for community-dwelling, but not institutionalized, patients.

STUDY POPULATION

The study population comprised of patients aged ≥ 50 years who suffered an incident hip fracture between 1 January 2000 and 31 December 2010 and who did not receive a prescription for any anti-osteoporosis drug (bisphosphonates, calcitonin, strontium ranelate, raloxifene, parathyroid hormone analogues [teriparatide]) in the 6 months prior to the index hip fracture. A 6-month period was chosen since previous studies have shown that the vast majority of patients who stop with anti-osteoporosis treatment restart their treatment within 6 months[25] and is also in line with previous studies.[16] To ensure that the hip fracture was the first hip fracture, patients with a record of non-specified fractures any time prior to the index hip fracture date were excluded. Approval for this study was given by the Independent Scientific Advisory Committee for MHRA Database Research (protocol number 13_113, amendment 2).

OUTCOME

The outcome of interest was a prescription for an anti-osteoporosis drug in the year following hip fracture. This was defined as a prescription for either: bisphosphonates (alendronic acid, risedronic acid, ibandronic acid, etidronic acid and zoledronic acid), calcitonin, strontium ranelate, raloxifene or parathyroid hormone analogues (teriparatide) based upon the NICE guidelines for secondary osteoporosis treatment.[26] Additionally, prescribing trends for calcium/vitamin D (separately and in combination with anti-osteoporosis drugs) and hormone replacement therapy (HRT) were described. Patients were followed from the date of index hip fracture until the date of the first prescription or censoring, whichever came first. Patients were censored upon death, exit from the database or end of the follow-up period (365 days after the index hip fracture, 31 December 2011 at the latest).

DETERMINANTS

Factors identified as potential determinants for anti-osteoporosis drug prescribing were largely based on risk factors for osteoporosis or fracture: age, sex, smoking status (non-smoker, ex-smoker, current smoker, missing), the most recent record of body mass index ([BMI]; <18, 18–25, >25 kg/m^2, missing), history of major fracture (clinical vertebrae, forearm, humerus), falls (3–12 months before), a history of secondary osteoporosis in accordance with the FRAX definition,[27] inflammatory bowel disease (Crohn's disease and ulcerative colitis), rheumatoid arthritis, Parkinson's disease, cerebrovascular disease, ischemic heart disease, and the use in the 6 months prior of corticosteroids, antipsychotics, antidepressants, opioid analgesics stronger than tramadol, anticonvulsants and benzodiazepines and other sedatives/hypnotics or calcium/vitamin D. In addition to these, a history of dementia or malignant neoplasms and the total number of different prescriptions (poly-pharmacy) in the 6 months prior to hip fracture may also influence prescribing practice. Indication for osteoporosis treatment is historically based on bone mineral density (BMD); however, this data is not routinely available within the CPRD and so could not be included in this analysis.

STATISTICAL ANALYSIS

Sex-specific descriptive characteristics were calculated at baseline. Kaplan-Meier life-table analyses were used to estimate the cumulative incidence probability for receiving a prescription for anti-osteoporosis drugs within 1 year of hip fracture. The analysis was done separately for each calendar year and stratified by age categories (50–74, 75–84, ≥ 85 years), region (England, Scotland, Wales and Northern Ireland) and sex. We also examined prescribing trends over time for the individual drug classes, type of bisphosphonate, and for calcium/vitamin D both separately and in combination with anti-osteoporosis drugs. For the latter analysis, patients were required to not have received both anti-osteoporosis drugs and calcium/vitamin D in the 6 months before hip fracture.

Univariate and multivariate Cox proportional hazard models were used to identify which factors (including the year of index hip fracture) were determinants of anti-osteoporosis drug initiation. Since for some of the covariates' (BMI, smoking status) missing data were present, multiple imputation was used to create five imputed datasets. Analyses were performed separately for the five imputed datasets, and hazard ratios (HRs) were pooled using the MIANALYZE procedure. All analyses were carried out using SAS 9.2 (SAS, Cary NC, USA).

RESULTS

TRENDS IN ANTI-OSTEOPOROSIS DRUG PRESCRIBING

Over the 10-year period, 30 516 patients aged 50 years or older suffered a hip fracture. Of these, 2974 (9.7%) had received at least one prescription for anti-osteoporosis drugs in the 6 months prior to the index fracture. Table 1 shows the characteristics of the study population. The median age (interquartile range) was 83 (76–88) and 79 years (71–85) for females and males, respectively.

After index hip fracture, 6684 patients received some form of anti-osteoporosis therapy, of which 94% of the prescriptions were for bisphosphonates. The mean time to receiving a prescription was 88 days (SD 80). The remaining patients, 20 858 (68%), had no record of receiving osteoporosis medication in either the 6 months prior or in the year following hip fracture.

During the study period, there was a steady rise in anti-osteoporosis drug prescribing following a hip fracture. Among patients who were not currently on treatment, the probability of receiving an anti-osteoporosis drug increased from 7.4% in 2000 to 45.5% in 2010. Cumulative incidence of receiving anti-osteoporosis drugs was greater at any given point in time in women compared to men. The proportion of women that was prescribed an anti-osteoporosis drug in 2000 was 8.2% and increased to 51.3% in 2010. These numbers were 4.1% and 33.6% for men, respectively. By 2010, a female hip fracture patient was 1.5 times more likely to be prescribed an anti-osteoporosis drug when compared to males (Figure 1a). Figure 1b demonstrates that this trend also differed between age categories, with a more pronounced trend for patients aged 75 years and older than for those under the age of 75 years, particularly after 2005 where the prescribing rates continued to increase for the older population but stabilized for patients under the age of 75 years. Figure 1c shows that there was a general improvement in anti-osteoporosis prescribing for all four UK regions (England, Scotland, Wales and Northern Ireland), but levels of prescribing varied considerable across these regions. From 2008, these rates diverged with an increase in Northern Ireland and a decrease in Scotland.

TABLE 1 | Baseline characteristics of hip fracture patients who were not in receipt of anti-osteoporosis drugs

Characteristic	Male (n=7051)		Female (n=20 491)		Total (n=27 542)	
Age category, n, %						
50-74	2348	33.3	4177	20.4	6525	23.7
75-84	2801	39.7	7860	38.3	10 661	38.7
85+	1902	27.0	8454	41.3	10 356	37.6
BMI category (kg/m^2), n, %						
< 18	590	8.4	2547	12.4	3137	11.4
18 - 25	2390	33.9	6384	31.2	8774	31.9
>25	2470	35.0	5703	27.8	8173	29.7
Missing [a]	1601	22.7	5857	28.6	7458	27.1
Smoking category, n, %						
Non-Smoker	2393	33.9	10 595	51.7	12 988	47.2
Ex-smoker	2068	29.3	3010	14.7	5078	18.4
Current Smoker	1879	26.7	4058	19.8	5937	21.6
Missing [a]	711	10.1	2828	13.8	3539	12.8
Disease history, n, %						
≥ 1 fall (3 – 12 months prior hip fracture)	494	7.0	1792	8.7	2286	8.3
History of major fracture	689	9.8	4152	20.3	4841	17.5
Secondary osteoporosis [b]	511	7.2	1023	5.0	1534	5.6
Inflammatory bowel disease	95	1.3	224	1.1	319	1.2
Rheumatoid arthritis	160	2.3	652	3.2	812	2.9
Parkinson's disease	368	5.2	579	2.8	947	3.4
Dementia	679	9.6	2747	13.4	3426	12.4
Cerebrovascular disease	1545	21.9	3444	16.8	4989	18.1
Ischemic heart disease	1683	23.9	3624	17.7	5307	19.3
Malignant neoplasms	1296	18.4	2818	13.8	4114	14.9
Drugs history (6 months prior), n, %						
Antipsychotics	445	6.3	1667	8.1	2112	7.7
Antidepressants	1323	18.8	4945	24.1	6268	22.8
Anti-epileptics	403	5.7	810	4.0	1213	4.4
Corticosteroids	1249	17.7	2907	14.2	4156	15.1
Opioid Analgesics	1248	17.7	3933	19.2	5181	18.8
Sedatives and Hypnotics	1004	14.2	4074	19.9	5078	18.4
Calcium/vitamin D	360	5.1	2069	10.1	2429	8.8
Hormone replacement therapy	3	0	274	1.3	277	1.0
Number of different prescriptions, n, %						
< 5	2110	29.9	6285	30.7	8395	30.5
5-9	2300	32.6	7214	35.2	9514	34.5
10-14	1490	21.1	4198	20.5	5688	20.7
> 14	1151	16.3	2794	13.6	3945	14.3

[a] Imputed values were used for regression models
[b] As defined by FRAX; anorexia nervosa, coeliac disease, diabetes mellitus (type 1), hypogonadism, osteogenesis imperfecta, osteomalacia, liver disease (cirrhosis, hepatitis, and neoplasms), malnutrition, malabsorption, and premature menopause.

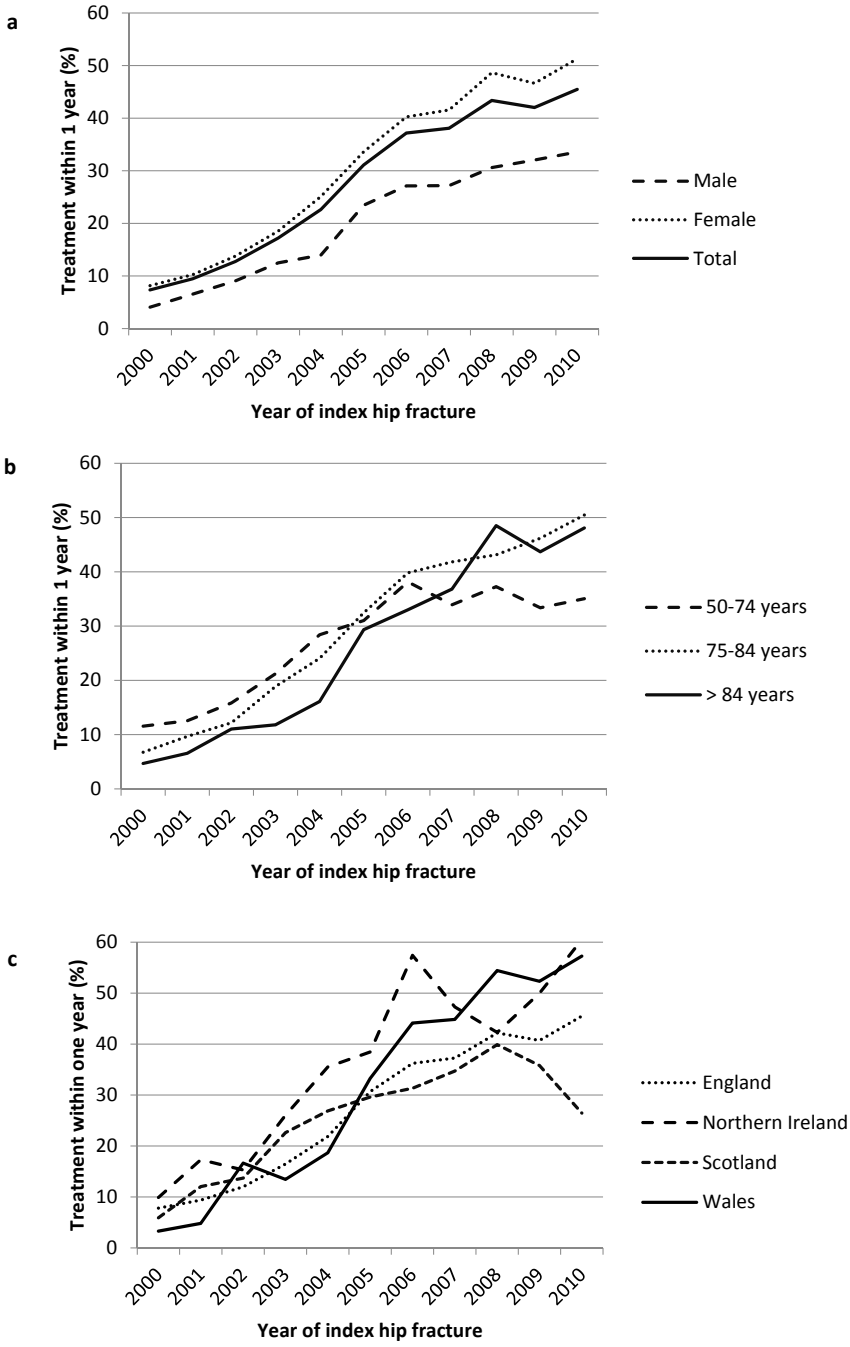

FIGURE 1 | Trends in anti-osteoporosis drug prescribing after hip fracture (by Kaplan-Meier method), stratified by sex (a), age categories (b) and region (c).

Evaluation of the medication classes individually demonstrated a substantial rise in the prescribing of bisphosphonates within 1 year after hip fracture (Figure 2a). Figure 2b shows the trend in the prescribing of bisphosphonates, stratified by the type of bisphosphonate. Alendronic acid was the most frequently prescribed bisphosphonate followed by risedronic acid, and after 2006, this disparity became markedly greater. Zoledronic acid was not included in the figure as numbers were too low (n = 2). Finally, from Figure 3, it can be seen that there has been a dramatic increase in the combined prescribing of anti-osteoporosis drugs together with vitamin D/calcium supplementation.

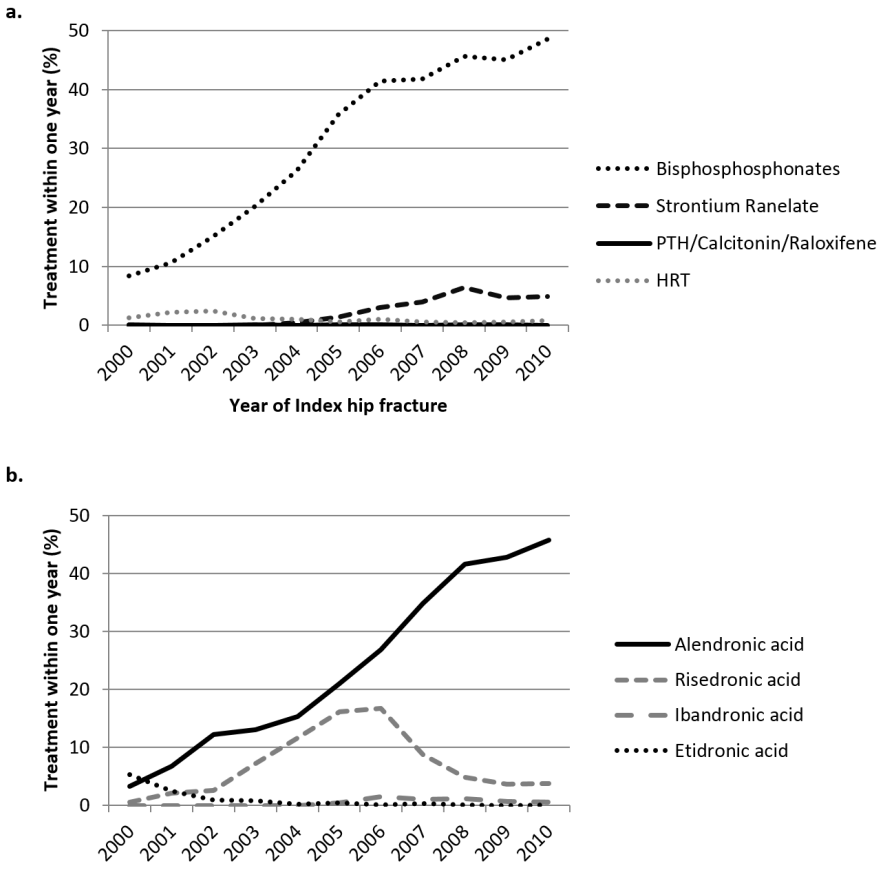

FIGURE 2 | Trends in anti-osteoporosis drug prescribing after hip fracture (by Kaplan-Meier method), stratified by drug class (a) and type of bisphosphonate (b)

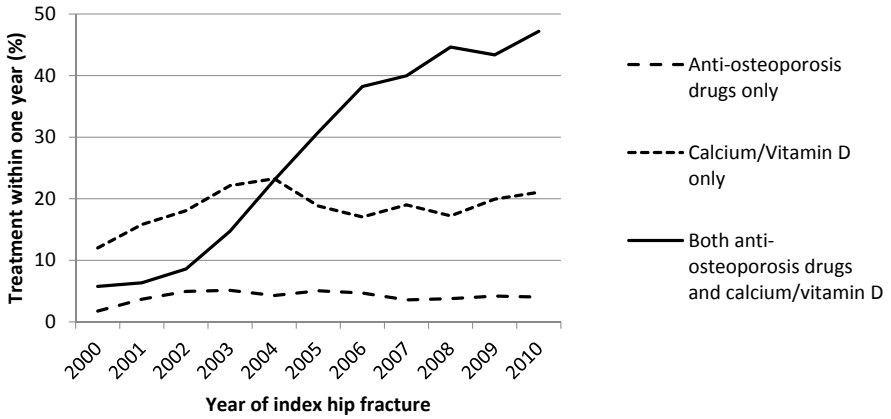

FIGURE 3 | Trends in anti-osteoporosis drug and calcium/vitamin D prescribing individually or combined (by Kaplan-Meier method).

DETERMINANTS OF ANTI-OSTEOPOROSIS DRUG PRESCRIBING

Multivariable Cox regression identified increased likelihood of being prescribed an anti-osteoporosis drug after hip fracture for increasing calendar year, female sex (adj. HR 1.74, 95% confidence interval (CI) 1.64–1.86), rheumatoid arthritis (adj. HR 1.26, 95% CI 1.11–1.42) and the presence of secondary osteoporosis (adj. HR = 1.13, 95% CI 1.03–1.26), corticosteroid use and a history of major osteoporotic fracture. When compared to patients younger than 60 years, patients between the ages of 60–90 years were significantly more likely to receive osteoporosis therapy. Conversely, having dementia, a BMI > 25 kg/m^2 or using antipsychotics, sedatives/hypnotics, or opioid analgesics were negatively associated with the initiation of osteoporosis therapy (Table 2).

TABLE 2 | Cox proportional hazard ratios (95% CI) for anti-osteoporosis drug initiation within 12 months of incident hip fracture.

Characteristic	Age-sex-adjusted HR (95% CI)		Fully adjusted HR (95% CI)	
Index year of hip fracture				
2001 vs. 2000	1.33	(1.05-1.68)	1.33	(1.06-1.68)
2002 vs. 2000	1.88	(1.51-2.33)	1.88	(1.51-2.34)
2003 vs. 2000	2.60	(2.12-3.18)	2.61	(2.13-3.20)
2004 vs. 2000	3.54	(2.91-4.32)	3.57	(2.93-4.36)
2005 vs. 2000	5.46	(4.51-6.62)	5.49	(4.53-6.66)
2006 vs. 2000	6.79	(5.61-8.21)	6.83	(5.65-8.27)
2007 vs. 2000	7.15	(5.91-8.64)	7.19	(5.95-8.70)
2008 vs. 2000	8.50	(7.04-10.3)	8.72	(7.21-10.5)
2009 vs. 2000	8.50	(7.02-10.3)	8.63	(7.13-10.5)
2010 vs. 2000	9.77	(8.08-11.8)	9.87	(8.15-11.9)
Age (years)				
60-69 vs. 50-59	1.10	(0.96-1.26)	1.18	(1.03-1.35)
70-80 vs. 50-59	1.21	(1.08-1.37)	1.48	(1.30-1.67)
80-89 vs. 50-59	1.19	(1.05-1.33)	1.43	(1.73-1.61)
≥ 90 vs. 50-59	0.89	(0.78-1.02)	1.04	(0.91-1.20)
Gender				
Female vs. male	1.52	(1.43-1.62)	1.74	(1.64-1.86)
BMI category (kg/m^2)				
< 18 vs. 18 - 25	0.93	(0.83-1.04)	0.95	(0.84-1.07)
> 25 vs. 18 - 25	0.87	(0.83-0.92)	0.86	(0.82-0.91)
Smoking category				
Ex-smoker vs. non-Smoker	1.16	(1.09-1.24)	0.98	(0.92-1.05)
Current Smoker vs. non-Smoker	0.84	(0.79-0.90)	1.00	(0.93-1.07)
Disease history [a]				
≥ 1 fall (3 – 12 months prior)	0.94	(0.86-1.04)	0.91	(0.83-1.00)
History of major fracture	1.13	(1.07-1.21)	1.12	(1.05-1.19)
Secondary osteoporosis	1.23	(1.12-1.36)	1.13	(1.03-1.26)
Inflammatory bowel disease	1.16	(0.94-1.43)	1.03	(0.83-1.27)
Rheumatoid arthritis	1.31	(1.16-1.48)	1.26	(1.11-1.42)
Parkinson's disease	0.94	(0.82-1.08)	1.03	(0.90-1.18)
Dementia	0.66	(0.61-0.72)	0.65	(0.59-0.71)
Cerebrovascular disease	0.96	(0.90-1.02)	0.99	(0.93-1.06)
Ischemic heart disease	1.01	(0.95-1.07)	0.98	(0.92-1.04)
Malignant neoplasms	1.03	(0.96-1.10)	0.92	(0.87-1.00)
Drug history [a] (in 6 month prior to hip fracture)				
Antipsychotics	0.53	(0.47-0.60)	0.66	(0.58-0.74)
Antidepressants	0.95	(0.89-1.00)	0.98	(0.92-1.04)
Anti-epileptics	1.02	(0.90-1.14)	0.96	(0.85-1.08)
Corticosteroids	1.22	(1.14-1.30)	1.16	(1.08-1.25)
Opioid analgesics	0.86	(0.80-0.91)	0.93	(0.86-0.99)
Sedatives and hypnotics	0.83	(0.77-0.88)	0.92	(0.86-0.99)
Calcium/vitamin D	1.21	(1.12-1.31)	1.04	(0.96-1.13)
Number of prescriptions	1.01	(1.01-1.01)	1.00	(0.99-1.01)

Abbreviations: HR hazard ratio, CI confidence interval, BMI body mass index
[a] Reference category is no history of disease or exposure to a drug

DISCUSSION

The last decade has seen a striking change in prescribing practices for anti-osteoporosis drugs following a hip fracture. The probability of initiating anti-osteoporotic treatment has increased dramatically, particularly for patients over the age of 75 years. It was also apparent that the initiation of anti-osteoporosis drugs was paired with the initiation of calcium/vitamin D supplementation. However, this encouraging trend slowed down from 2006 onwards. Ultimately, the overall prescribing rate has remained inadequate with just over 50% of hip fracture patients not receiving any anti-osteoporosis drug in 2010. The factors which were associated with reduced likelihood of receiving anti-osteoporosis drug therapy were male gender, being overweight, having dementia or exposed to certain psychotropic drugs (antipsychotics, sedatives/hypnotics) or opioid analgesics.

Our findings of a steady increase in the prescribing of anti-osteoporosis drugs up until 2005 are consistent with most studies performed in other countries[15-19] and form an extension to the study performed on the former version of the CPRD (GPRD) for the period 1991–2005 by Watson et al.[20] The pattern of anti-osteoporosis drug prescribing may be reflective of changes in bisphosphonate formulation, advice from various committees and changes to NHS guidelines. As from 2005, there was a pronounced difference in prescribing of anti-osteoporosis medications between patients under and over 75 years. This is most likely a consequence of the NICE Technology Appraisal 87 published in 2005,[28] which advocated the use of anti-osteoporosis therapies without the need for prior dual energy X-ray absorptiometry (DXA) scanning for women over the age of 75 years who had already suffered a hip fracture. This, however, does not explain why the prescribing rate plateaued for those <75 years. We have no clear explanation for this phenomenon, but it may be partly related to the actual proportion of hip fractures that was attributable to osteoporotic BMD. This proportion has been reported to range between 28% and 64 %, depending on age and sex.[29,30] Since DXA-derived diagnosis of osteoporosis has been the cornerstone for indicating anti-osteoporosis drug therapy, an increase in DXA referrals may not necessarily have resulted in a further increase in anti-osteoporosis drug prescribing as osteoporosis may subsequently not have been diagnosed for many younger hip fracture patients. Furthermore, the cost of anti-osteoporotic drugs has been reduced further since the release of generic forms of alendronic acid in August 2005. Subsequently, NICE guidance (TA161) endorsed alendronic acid as the first-line therapy. This resulted in the stabilization in the prescribing of risedronic acid in 2005 whose use then went into decline.[26] The majority of anti-osteoporosis drug prescribing was paired with the prescribing of vitamin D/calcium supplements which is in line with clinical guidelines. Another UK study that was conducted in 2006 among nine general practitioner practices showed that 34 % of patients were co-prescribed calcium and/or vitamin D with anti-osteoporosis drugs.[23] This coincides well with our results with a cumulative incidence probability of 39% in 2006. Unfortunately, there was a considerable number of patients who only received vitamin D/calcium supplementation.

In line with the results by Wang et al.,[31] we found a slowing down in the increasing prescribing trend from 2006 onwards, while an Australian study showed a decline between 2007 and 2010.[32] Reasons for the stagnation or even decline in anti-osteoporosis drug prescribing may coincide with revised labelling of bisphosphonates for risk of osteonecrosis of the jaw in 2005 and reports for increased risk of atypical femoral fractures and atrial fibrillation, with increasing publicity in the years thereafter. A US study showed a decline in use of anti-osteoporosis drugs after hip fracture from 2002 onwards (40.2% in 2002 to 20.5% in 2011).[12] Together with the possible influence of safety issue reports, this could have been attributed to a fragmented health care system with a lack of, or insufficient, communication between emergency/orthopedic departments and outpatient care for follow-up osteoporosis assessment. A service model to bridge this gap, the Fracture Liaison Service (FLS), now exists for over a decade in the UK which has proven to reduce the care gap for secondary fracture prevention.[33] However, this care model has been developed in 27% of UK NHS Hospital Trusts prior to 2006, which has barely increased to 29% by 2009. This is in line with the flattening in prescribing rates for this period.

Few studies have examined which factors lead to the initiation of anti-osteoporosis drugs after hip fracture. Many of the factors which increase the risk of fracture were also significant determinants for initiation of anti-osteoporosis drug therapy. Hence, female gender, increasing age (except for very old age), a history of major osteoporotic fracture, rheumatoid arthritis, secondary osteoporosis and the use of corticosteroids all increased the likelihood of receiving osteoporosis treatment which is in line with previous studies.[12,34-37] Conversely, patients who were suffering from mental illness (i.e. using antipsychotics, sedatives and hypnotics or having dementia) or patients who were overweight or used opioid analgesics were less likely to receive osteoporosis therapy. Other factors which have been associated with the initiation of anti-osteoporosis drug treatment are patients' self-perception of osteoporosis risk[34] and their appraisal for their treatment need,[38] but these could not be identified in our data. The fact that an increasing number of prescriptions was not inversely associated with the instigation of osteoporosis therapy was unexpected given the findings of Duyvendak *et al.*[39] who found that poly-pharmacy was a barrier to osteoporosis treatment in long-term corticosteroid users. The study of Solomon *et al.*[12] even found an increased likelihood of being prescribed anti-osteoporosis drugs with increasing number of prescriptions which was also conducted among hip fracture patients. Consistent with other findings is the observation that male hip fracture patients were less likely to be prescribed anti-osteoporosis drugs than female patients. [12,16,40] The difference in prescribing patterns between men and women is likely partly due to osteoporosis primarily being considered a health problem of older women,[41,42] rather than of men; consequently, men often have poor knowledge of the condition and therefore do not consider themselves as susceptible[43,44] and hence would not consider asking their GP for treatment. Furthermore, the number of clinical trials examining the effect of bisphosphonates on fracture reduction in men is limited, where the majority of trials used

change in bone mineral density (BMD) as the primary end point.[45,46] The few trials into the effects of bisphosphonate use on fracture reduction in men and lack of clinical guidance for anti-osteoporosis drug prescribing for men may explain why GPs do not habitually provide bisphosphonate treatment to men. However, seeing as the bisphosphonate has a similar effect on bone turnover and density in both men and women, the difference in prescribing habits is likely unjustified.

We studied a large community-dwelling population representative of the UK as a whole. However, there are several limitations that should be considered in the interpretation of our results. By studying hip fracture patients, we have assumed that all of our study population was eligible for anti-osteoporosis medication according to a confirmed diagnosis of osteoporosis, while this may not necessarily have been the case. BMD measurements are not routinely available in the CPRD which limits our interpretation as to the eligibility for treatment. Additionally, it is possible that some fractures were pathological or due to trauma. Furthermore, we have only considered initial prescription rates and did not include repeat prescriptions. Therefore, we cannot make any comments regarding adherence with treatment. It is well known that a large proportion of patients do not adhere to their treatment regimen, although the exact reasons for this phenomenon remain poorly understood.[47] Zoledronic acid as well as PTH analogues (teriparatide) and denosumab are not fully captured in CPRD records as this database only includes prescriptions issued by general practitioners and not specialists. This may have resulted in an underestimate of anti-osteoporosis therapy initiation. However, denosumab became available in the UK at the end of the study period (2010), and although we cannot directly estimate the magnitude of this limitation for PTH analogues and zoledronic acid, indirect evidence from other countries has shown that the utilisation of these drugs remained limited until the year 2010.[12,32] Furthermore, NICE guidance places teriparatide under restrictive conditions for the secondary prevention of fragility fractures. Similarly, data for non-prescription over-the-counter vitamin D or calcium were not available in our database, which may have resulted in an underestimate of use of these drugs. Finally, the generalisability of this study is limited to free-living individuals as it excluded those who were institutionalized. Just under 10 % of the patients transferred out of the database, most likely to nursing homes where prescribing practices could differ.

In conclusion, our study has shown that although the prescribing rate for anti-osteoporosis medications has increased substantially since 2000, the overall rate in 2010 was still markedly inadequate. This was particularly so in men, where the prescribing of anti-osteoporosis drugs was notably less than that observed in women at any given point in time. Other patient characteristics that were associated with decreased likelihood of receiving anti-osteoporosis drugs were being overweight, having dementia and exposed to antipsychotics, sedatives/hypnotics or opioid analgesics. Increase in the prescribing of anti-osteoporosis medications may be facilitated by recent major advances in risk assessment, such as the FRAX calculator,[48]

linked to treatment thresholds, as exemplified by the UK NOGG Guidelines.[49] There is much work to promote secondary fracture prevention services,[50] notably by the current International Osteoporosis Foundation Capture the Fracture initiative.[51] With the absolute number of hip fractures expected to increase inexorably across the world over coming decades, our findings clearly demonstrate the acute need for such activity and for the generally increased awareness of osteoporosis and prevention of fragility fracture.

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CHAPTER 4.2

Long-term persistence with anti-osteoporosis drugs after fracture

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ABSTRACT

Summary: Long-term persistence with anti-osteoporosis drugs and determinants for discontinuation among fracture patients were examined. Persistence was 75.0% and 45.3% after 1 and 5 years, respectively. Those aged ≥ 80 years were at increased risk of early discontinuation. Within 1 year after discontinuation, 24.3% restarted therapy, yet 47.0% persisted for 1 year.

Introduction: The risk of osteoporotic fracture can effectively be reduced with use of anti-osteoporosis drugs. However, little is known about persistence with these drugs after fracture where subsequent fracture risk is high. The aims were to determine long-term persistence with anti-osteoporosis drugs among fracture patients, including its determinants, and to describe restart and subsequent persistence.

Methods: A cohort study was conducted within the Dutch PHARMO Database Network. Patients aged ≥ 50 years (n=961) who received anti-osteoporosis drugs within 1 year after fracture, but not in the preceding year, were included (2002–2011). Persistence (defined as the proportion on treatment) and the proportion restarting after discontinuation were estimated using Kaplan-Meier analyses. Time-dependent Cox regression was used to identify determinants of non-persistence including age, sex, initial dosage regime, fracture type, comorbidities, and drug use.

Results: Persistence with anti-osteoporosis drugs was 75.0% (95% confidence interval (CI) 72.0–77.7) and 45.3% (95% CI 40.4–50.0) after 1 and 5 years, respectively. A significant determinant of non-persistence was age ≥ 80 years (reference 50–59 years: adjusted hazard ratio [adj. HR] 1.65; 95% CI 1.15–2.38).This effect was not constant over time (≤ 360 days following initiation: adj. HR 2.07; 95% CI 1.27–3.37; > 360 days: adj. HR 1.08; 95% CI 0.62–1.88). Within 1 year after discontinuation, 24.3% (95% CI 20.1–29.2) restarted therapy, yet 47.0% persisted for 1 year.

Conclusions: This study identified suboptimal persistence with anti-osteoporosis drugs among fracture patients. Major target groups for measures aimed to improve persistence may be those aged ≥ 80 years and those restarting therapy.

INTRODUCTION

Osteoporotic fractures are a major burden for the patient in terms of increased morbidity, mortality and a reduction in quality of life.[1] Prior fractures are strong predictors of fracture risk. Indeed, the fracture risk is two-fold higher following a non-vertebral fracture and is quadrupled after a vertebral fracture.[2] This risk is not constant over time with a fivefold higher risk in the year after the first fracture followed by a gradual waning off.[3] Within 5 years after the initial fracture, up to one third of the patients will sustain a new fracture.[4,5] Anti-osteoporosis drugs, of which bisphosphonates are the most commonly prescribed, have shown to reduce the relative risk of osteoporotic fractures by 20–70% in clinical trials, depending on the drug and fracture type.[6-8]

Persistence with therapy is an important determinant for the anti-fracture efficacy of anti-osteoporosis drugs in clinical practice.[9-12] A meta-analysis with data of 219 676 patients indicated that non-persistence with anti-osteoporosis drugs increased fracture risk by 32% (hazard ratio (HR) 1.32; 95% confidence interval (CI) 1.23–1.42) where follow-up between studies varied between 40 and 159 weeks.[9] The effectiveness of oral bisphosphonates in relation to duration of use was more specifically identified in a Dutch observational study; persistent use of oral bisphosphonates for 1–2 and 3 –4 years reduced fracture risk by 12% and 46%, respectively, compared to < 1 year of use (OR 0.88, 95% CI 0.66–1.18 and OR 0.54, 95% CI 0.35–0.84, respectively).[12] Real-world persistence with osteoporosis therapy is, however, poor. One-year persistence ranged from 18% to 78% between studies where differences were at least partly arising from non-uniformity used for the operational definition of persistence, including data-derived persistence and self-report.[13-20] While previous studies have been conducted among first time users of anti-osteoporosis drugs, there is a lack of understanding on fracture history with few studies identifying patients who had (recently) sustained an osteoporotic fracture. As a previous fracture is one of the most important risk factors for a subsequent fracture, it is important to investigate persistence with anti-osteoporosis drugs in this patient group and to understand its determinants. Furthermore, little is known about restart and subsequent persistence with these drugs after first discontinuation. Therefore, the aims of this study were (1) to identify long-term persistence with anti-osteoporosis drugs and its determinants in patients who had recently sustained a major osteoporotic fracture (hip, clinical vertebrae, humerus, forearm), (2) to determine the frequency of restarting treatment among patients who discontinued use, and (3) to assess persistence after restarting anti-osteoporosis treatment.

METHODS

DATA SOURCE

A cohort study was performed within the Dutch PHARMO Database Network [PHARMO Institute for Drug Outcome Research, www.pharmo.nl]. This data source contains primary care data linked to outpatient pharmacy dispensing data, hospitalizations from the Dutch Hospital Data Foundation (DHD, www.dutchhospitaldata.nl) and death registration data for approximately 660 000 community-dwelling individuals in the Netherlands. Almost every individual in the Netherlands is registered with a single community pharmacy, which results in a high degree of completeness with regard to dispensed drugs.[21] Drug-dispensing records contain information concerning the dispensed drug according to the Anatomical Therapeutic Chemical (ATC) Classification system codes including amount, dose, dosage regime, and date of dispensing. Primary care diagnoses are coded according to the International Classification of Primary Care (ICPC) coding system. Hospital records include dates of hospital admission and discharge, diagnoses, and procedures recorded according to the International Classification of Disease, 9th or 10th revision codes (ICD-9 or ICD-10).

STUDY POPULATION

All patients ≥ 50 years with a first record of a hip, humerus, clinical vertebral, or forearm fracture since the start of data collection were identified. Fractures were extracted from primary care records and hospitalization data between 1 January 2002 and 31 December 2011. In the Netherlands, drugs available for the treatment of osteoporosis include bisphosphonates (alendronic acid, risedronic acid, etidronic acid, ibandronic acid, zoledronic acid), selective estrogen receptor modulators (SERMS; raloxifene, bazedoxifene), strontium ranelate, teriparatide, and denosumab. Patients were included at the date of first dispensing for an anti-osteoporosis drug in the year following the first fracture but not in the preceding year to include incident users only. The date of the first dispensing of an anti-osteoporosis drug after the fracture was set as the index date. Patients who were dispensed clodronic acid, pamidronic acid, tiludronic acid, or risedronic acid 30 mg once daily were not included since these drugs are not registered for osteoporosis but for hypercalcemia during malignancy or Paget's disease, which may also increase fracture risk. In the Netherlands, repeated weekly dispensing of medications is an indicator of medication delivery by a "weekbox," suggesting that patient persistence is monitored by a health care professional, and thus, any discontinuation is likely not patient driven. To control for physician-directed discontinuation, patients with repeated weekly (7-day) dispensing records were excluded.

STUDY OUTCOMES

The outcome of interest was persistence with any anti-osteoporosis drug. Persistence was defined as the proportion of patients who were on treatment since treatment initiation.[22] Assessment of persistence was based on the calculation of the total duration of use where

switching between drugs and dosage regimes was permitted.[23] The total duration of use was calculated on the basis of subsequent prescriptions for anti-osteoporosis drugs that were collected by (i.e., dispensed to) the patient at the community pharmacy. For each pharmacy dispensing, the theoretical duration of use was calculated by dividing the amount dispensed by the prescribed dosage regime. In the event of overlap between two dispensings (i.e., a repeat dispensing within the duration of use of a previous dispensing), the overlap days were added to the duration of the repeat dispensing. A gap of 90 days between the theoretical end date of a pharmacy dispensing (defined as the date of dispensing plus the theoretical duration of use) and the subsequent dispensing date was allowed. A patient was therefore classified as having discontinued with anti-osteoporosis treatment when either a gap of >90 days occurred between two dispensings, or when no further dispensing was issued and at least 90 days were available to the right censoring date. A 90-day permissible gap is consistent with prior literature,[14,15] and the maximum amount dispensed is a 90 days' supply in the Netherlands for chronic treatment, which is required for osteoporosis.[23,24] In sensitivity analyses, permissible treatment gaps of 180, 270, and 365 days were applied. Among patients who discontinued use using a 90-day permissible gap, the proportion restarting therapy was identified. Persistence with any anti-osteoporosis drug upon restart of therapy was determined similarly as described above.

DEFINITION OF COVARIATES

Potential determinants of non-persistence (discontinuation) with anti-osteoporosis drugs were included in univariate and multivariate Cox proportional hazards models. Age, drug exposure, and comorbidities were included as time-dependent covariates. Total follow-up time was divided into 30-day intervals, and covariates were evaluated before each interval. Covariates included age groups (50–59, 60–69, 70–79, ≥80 years), sex, type of fracture (hip, humerus, clinical vertebrae, forearm fracture), dosage regime of initial anti-osteoporosis drug (daily, weekly or monthly), drug use in the 6 months before (systemic glucocorticoids, antidepressants, non-selective anti-inflammatory drugs [NSAIDs], opioids [tramadol or stronger], calcium supplements and/or vitamin D, and disease-modifying anti-rheumatic drugs [DMARDs]), comorbidities included a diagnosis of dementia/Alzheimer's disease ever before, and the occurrence of upper gastrointestinal disorders or a subsequent fracture (at any site) in the 6 months before.[13,16,25] The presence of alcoholism was also considered, expressed by diagnosis codes for alcohol dependence and alcoholic liver diseases (alcoholic acute hepatitis, alcoholic liver cirrhosis, alcoholic liver damage, alcoholic fatty liver) or exposure to drugs for alcohol abstinence (disulfiram, acamprosate, nalmefene, naltrexone). An incident diagnosis of renal failure (diagnosis for renal failure or stage 4/5 chronic kidney disease) was assessed but occurred too infrequent to include into the analysis (n=3).

STATISTICAL ANALYSIS

All patients were followed from the index date until discontinuation, death, migration out of the data source, or end of study period [31 December 2011], whichever came first. Kaplan-Meier life table analyses were used to present persistence estimates (%) over time where discontinuation was the failure event. Analyses were completed using the whole study population and stratified by age groups and type of index fracture. Log-rank tests were used to test for significant differences between groups. In addition, Kaplan-Meier life tables were applied to determine the cumulative incidence of restarting any anti-osteoporosis drug after first 90-day discontinuation. Determinants of non-persistence were estimated by time-dependent Cox proportional hazards regression (PHREG procedure) by entering all covariates into the regression model. The proportional hazards assumption was tested by including time interaction terms into the model. In case of violation (p value interaction < 0.05), hazard ratios for the association between that covariate and non-persistence were calculated for two periods by restricting follow-up time to the first 12 30-day periods and the period thereafter (≤ 360 and > 360 days), to present the hazard ratio for "early" and "late" discontinuation, respectively. All statistical analyses were performed using SAS statistical software, version 9.2 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

A total of 1081 patients were identified as incident users of anti-osteoporosis drugs within 1 year after the first fracture. Of these, 120 patients had repeated 7-day dispensing indicating "weekbox" dispensing and were excluded. The final study cohort included 961 patients (81.3% female) with a mean age of 69.8 years (SD 9.6 years). The vast majority initially received a bisphosphonate (96.5%), most frequently alendronic acid (67.4%) or risedronic acid (29.7%). Alternatives for bisphosphonates, such as raloxifene and strontium ranelate, were rarely dispensed (Table 1). During follow-up, a total of 89 (9.3%) patients switched between types of anti-osteoporosis drugs, where 67.4 % of all switches occurred between alendronic acid and risedronic acid. Bisphosphonates were predominantly prescribed in a weekly dosage regime (94.2%). Of patients initiating on a daily dosage, 36.4% switched to another dosage regime during follow-up. Persistence estimates for treatment with anti-osteoporosis drugs are displayed in Figure 1a for the total study population. Persistence decreased from 75.0% (95 % CI 72.0–77.7) at 1 year to 45.3% (95 % CI 40.4–50.0) at 5 years following initiation. The median time on treatment was 4.6 years [95 % CI 4.1–5.0]. Increasing the gap length showed increases in persistence (Table 2). When stratified by age groups, significant differences in persistence were identified (p=0.003), with those aged 80 years and older at index date having the lowest persistence (Figure 1b), but no significant difference was noted between fracture types (p=0.17) (Fig. 1c). Of those aged 80 years and older, 63.9% (95 % CI 55.8–70.9) persisted for 1 year following treatment initiation, as compared to 82.8% (95 % CI 75.7–88.0) of those aged 50–59 years.

TABLE 1 | Characteristics of new anti-osteoporosis drug users who sustained a recent fracture

Characteristics	N = 961
Follow-up time, mean (SD), years	3.0 (2.1)
Female sex, n (%)	781 (81.3)
Age, mean (SD), years	69.8 (9.6)
Age categories, n (%)	
50 - 59	161 (16.8)
60 – 69	308 (32.0)
70 - 79	322 (33.5)
≥ 80	170 (17.7)
Type of index fracture, n (%)	
Proximal femur	204 (21.2)
Humerus	127 (13.2)
Clinical vertebral	322 (33.5)
Radius/ulna	308 (32.0)
Initial anti-osteoporosis drug, n (%)	
Bisphosphonate	927 (96.5)
Alendronic acid	624 (67.3)
Risedronic acid	275 (29.7)
Other bisphosphonate [a]	28 (3.0)
Strontium ranelate	29 (3.0)
Other [b]	5 (0.5)
Dosage regime, n (%)	
Daily	67 (7.0)
Weekly	873 (90.8)
Monthly	21 (2.2)
Diseases, n (%)	
Upper gastro-intestinal disorders six months before index date [c]	26 (2.7)
Dementia/Alzheimer's Disease ever before index date and during follow-up [c]	25 (2.6)
Alcoholism ever before index date and during follow-up [c]	24 (2.5)
Fracture at any site during follow-up	80 (8.3)
Upper gastro-intestinal disorders during follow-up	74 (7.7)
Drug use during six months before index date [c], n (%)	
Systemic glucocorticoids	78 (8.1)
Antidepressants	92 (9.6)
Opioids (tramadol or stronger)	97 (10.1)
Non-steroidal anti-inflammatory drugs	347 (36.1)
Calcium-supplements and/or vitamin D	64 (6.7)
Disease-modifying anti-rheumatic drugs	13 (1.4)

[a]Etidronic acid, ibandronic acid, [b] Raloxifene. [c] Index date defined as date of first dispensing for any anti-osteoporosis drug within one year after fracture

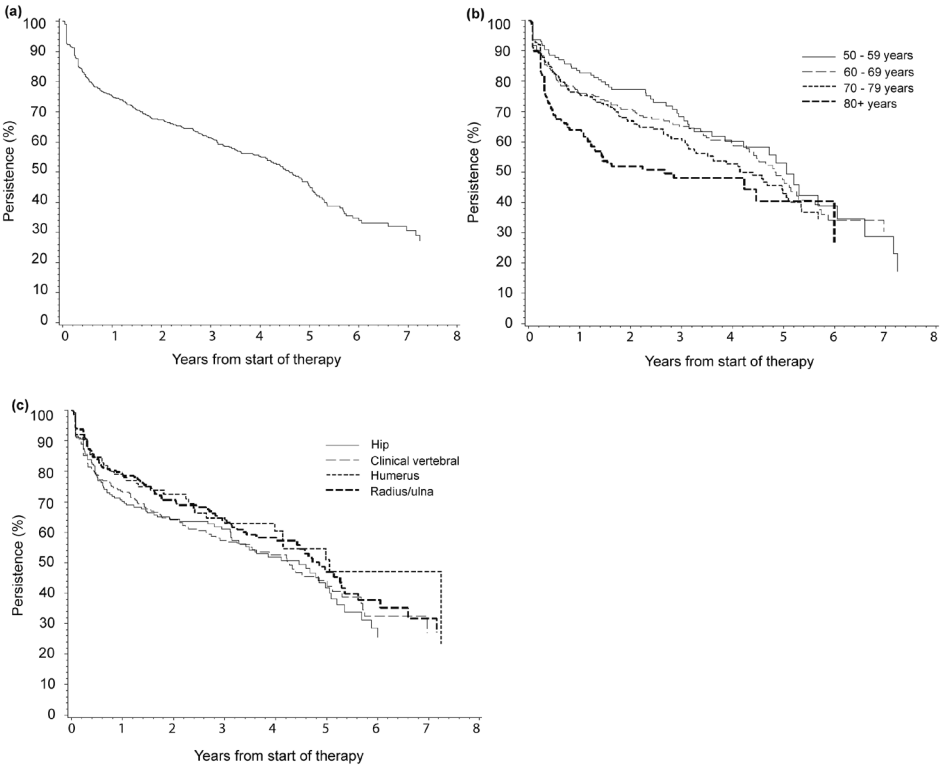

FIGURE 1 | Kaplan-Meier persistence curves for treatment with anti-osteoporosis drugs after a recent fracture for (a) the total study population, (b) stratified by age category, (c) stratified by type of fracture, – discontinuation was defined as a treatment gap of > 90 days and switching between anti-osteoporosis drugs or dosage regimes was allowed when this occurred within the treatment gap.

TABLE 2 | Kaplan-Meier estimates for persistence (%) at different time periods following initiation, by gap length

	Survival time [a]		
	1 year	3 years	5 years
Gap length			
90 days	75.0 (72.0 – 77.7)	61.3 (57.6 – 64.8)	45.3 (40.4 – 50.0)
180 days	79.2 (76.3 – 81.7)	68.2 (64.7 – 71.5)	53.6 (48.6 – 58.4)
270 days	82.2 (79.5 – 84.6)	73.0 (69.6 – 76.1)	58.9 (53.7 – 63.6)
365 days	84.4 (81.9 – 86.6)	75.2 (71.9 – 78.3)	64.4 (59.5 – 68.9)

[a] Patients were followed until first date of the following: discontinuation (non-persistence), death, migration out of the data source, or end of the study period.

Table 3 presents associations between the covariates and non-persistence with anti-osteoporosis drugs. In a multivariate model, age ≥ 80 years was identified as a significant determinant of discontinuation (reference 50–59 years; adjusted [adj.] hazard ratio [HR] 1.65; 95% CI: 1.15–2.38). The effect of age, however, was not constant over time (p value interaction < 0.05). When follow-up was restricted to the first 360 days following initiation,

persistence was significantly lower for those ≥ 80years as compared to those 50–59 years (adj. HR 2.07; 95% CI: 1.27–3.37), while this was not observed beyond 360 days of follow-up (adj. HR 1.08; 0.62–1.88). The association between an initial daily versus weekly dosage regime and non-persistence was also not constant over time (≤ 360 days; adj. HR 1.49, 95% CI 0.95–2.35, > 360 days; adj. HR 0.68; 95% CI 0.35–1.30, p value interaction < 0.05). Sensitivity analyses with increasing gap lengths provided similar results, where age ≥ 80 years remained the only significant determinant of non-persistence (see supplementary Table S1/S2/S3). Figure 2 shows the cumulative incidence of restarting any anti-osteoporosis drug after first discontinuation. Of all patients who discontinued treatment, 24.3% (95 % CI 20.1–29.2) restarted therapy within 1 year, and this increased to 40.4% (95 % CI 32.4–49.4) within 5 years. Patients who discontinued treatment were less likely to stay on treatment after restart; 47.0% (95% CI 36.4–56.9) persisted for 1 year. The median time on treatment was 0.92 years (95% CI 0.61–1.47) (Figure 3).

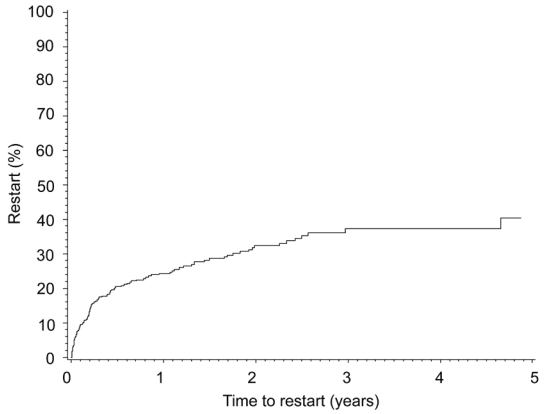

FIGURE 2 | Kaplan-Meier curve for cumulative incidence of restart with anti-osteoporosis drugs after first discontinuation (> 90-day gap)

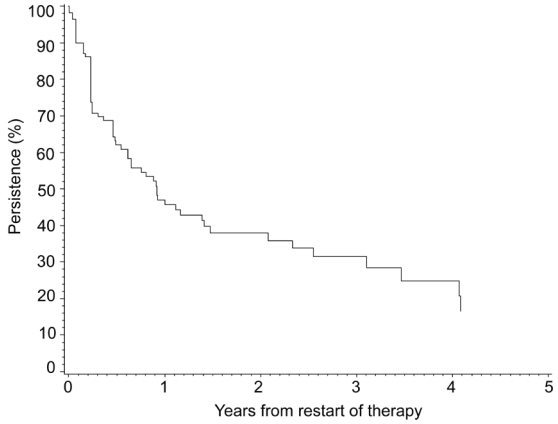

FIGURE 3 | Kaplan-Meier persistence curve for treatment with anti-osteoporosis drugs following restart of therapy (> 90-day gap)

TABLE 3 | Determinants of non-persistence (> 90-day gap) with anti-osteoporosis drugs after fracture

	Cr. HR (95% CI)	Adj. HR (95% CI)
Gender		
Male	Reference	Reference
Female	0.91 (0.71 – 1.18)	0.97 (0.74 – 1.26)
Age categories		
50 – 59 years	Reference	Reference
60 – 69 years	1.05 (0.75 – 1.47)	1.06 (0.76 – 1.50)
70 – 79 years	1.15 (0.82 – 1.60)	1.13 (0.80 – 1.58)
≥ 80 years	1.70 (1.20 – 2.42)	1.65 (1.15 – 2.38)
Type of index fracture		
Radius/ulna	Reference	Reference
Humerus	0.92 (0.65 – 1.31)	0.87 (0.61 – 1.23)
Clinical vertebral	1.22 (0.95 – 1.57)	1.13 (0.87 – 1.47)
Proximal femur	1.24 (0.94 – 1.63)	1.08 (0.81 – 1.44)
Dosage regime		
Once daily	1.21 (0.84 – 1.74)	1.06 (0.73 – 1.54)
Once weekly	Reference	Reference
Once monthly	0.58 (0.24 – 1.40)	0.58 (0.24 – 1.41)
Drug use [a]		
Systemic glucocorticoids	1.21 (0.84 – 1.73)	1.18 (0.82 – 1.70)
Antidepressants	1.12 (0.81 – 1.55)	1.11 (0.80 – 1.54)
Opioids (tramadol or stronger)	1.00 (0.65 – 1.53)	0.83 (0.53 – 1.29)
Non-steroidal anti-inflammatory drugs	1.01 (0.79 – 1.31)	0.98 (0.76 – 1.27)
Calcium supplements and/or vitamin D	0.96 (0.77 – 1.19)	0.94 (0.76 – 1.17)
Disease-modifying anti-rheumatic drugs	1.01 (0.48 – 2.14)	1.10 (0.52 – 2.34)
Disease occurrence [b]		
Dementia / Alzheimer's Disease	1.71 (0.94 – 3.11)	1.46 (0.79 – 2.70)
Subsequent fractures	1.70 (0.91 – 3.21)	1.64 (0.86 – 3.10)
Upper gastro-intestinal disorders	1.54 (0.79 – 3.00)	1.40 (0.71 – 2.74)
Alcoholism	1.55 (0.80 – 3.01)	1.50 (0.76 – 2.96)

Abbreviations: Cr; crude, Adj; adjusted, HR; Hazard Ratio, 95% CI; 95% Confidence Interval
[a] Reference group is no use within 6 months prior within that drug category
[b] Reference group is no occurrence within 6 months prior (ever prior for dementia/Alzheimer's Disease or alcoholism) within that disease category

DISCUSSION

In this cohort of newly treated fracture patients, persistence with anti-osteoporosis drugs decreased from 75% at 1 year to 45% at 5 years following initiation. Patients aged 80 years and older were at increased risk of early discontinuation. A substantial proportion of patients restarted treatment following first discontinuation; yet, 47% persisted with treatment for 1 year following restarting therapy.

Persistence estimates were higher than expected when compared to previously conducted studies among first-time users who did not initiate treatment specifically after fracture. A meta-analysis showed a pooled persistence estimate of 50% (95% CI 37–63) for treatment lasting 7 to 12 months as measured by treatment gaps that ranged from 30 to 120 days.[19] They also found increased persistence among patients allowed to switch medications (58% [95% CI 45–70] vs 46% [95% CI 38 –55]). Another study that was conducted among new users irrespectively of fracture status and that similarly defined persistence as the present study (90-day gap and allowed switching between drugs) found a 1-year persistence estimate of 67% (95% CI 66–68), which was still lower as compared to the current study.[15] This suggests that the setting, where treatment was initiated after a recent fracture, may have influenced persistence. Indeed, studies that included patients who visited fracture liaison services (FLSs) showed 1-year persistence that ranged between 74% and 88%, which were either based on self-report[25-28] or prescription claims.[29] These numbers may, however, have been biased upward by selection toward more motivated patients as only patients agreeing to participate in FLSs were included (response rate ranged between 38 and 88%). To the best of our knowledge, the only previously conducted population-based study that assessed persistence after fracture (1997–2004) showed a 1-year persistence estimate of 80% with alendronic acid weekly, etidronic acid, or raloxifene.[30] In a multivariable adjusted analysis, age of 80 years and older (reference 50–59 years) was identified as a significant determinant of non-persistence with anti-osteoporosis drugs early after initiation. This finding is in line with the, to the best of our knowledge, only previous study that explored determinants of non-persistence with these drugs when initiated after recent fracture (OR1.008; 95% CI: 1.004–1.012 per year of age).[30] Although older age was identified as a marker for increased risk of early discontinuation, the underlying reasons remain unknown and may be multifactorial, including but not limited to the number of comorbid conditions, poly-pharmacy, physical inability or dependency of others to take medication, or willingness to take medication. A weekly dosage regime has now been widely adopted in clinical practice and has been associated with increased persistence when compared to a daily regime although evidence is conflicting for the difference in persistence between weekly and monthly regimes.[13,17] In the present study, we did not find evidence that daily and monthly dosage regimes of the initial drug were associated with increased or decreased risk of discontinuation compared to a weekly regime, respectively. However, switching between anti-osteoporosis drugs and dosage regimes was permitted and may have diluted the association. In addition, the number of daily and monthly users was limited (daily, 7% of whom 3.4% were daily bisphosphonate users; monthly, 2.2%). Similarly, the occurrence of upper gastrointestinal disorders is a frequently cited reason for discontinuation of bisphosphonates, but this was not confirmed in the present study.[31-33] Again, switching between anti-osteoporosis drugs was allowed and may explain this finding. Furthermore, a qualitative study indicated that fear for side effects, while they did not occur yet, was enough to discontinue with treatment, which was not captured in our data.[26] Approximately 40% of patients restarted therapy within 5 years after discontinuation, of whom the majority did so

within the first 6months. Previous studies showed proportions of restarting patients varying between 18 and 38% within 6 months after first discontinuation.[13,18,34-36] Our finding of 20% is at the lower end of this range and is in agreement with a Dutch study, where 18% of osteoporotic patients restarted therapy within 6 months.[13] The substantial proportion of patients who restarted therapy was reflected by an increase in persistence over time when permissible treatment gaps became wider. The present study identified that persistence with anti-osteoporosis therapy was poor among restarting patients. While there is little evidence of persistence after restarting therapy, the results of this study are similar to, to our knowledge, the only previous study to address this issue, which identified a median duration of persistence of 6 months following restart (> 60-day gap).[18]

Strengths of this study include that persistence was determined over a long-term follow-up period and that linkage of longitudinal data of hospitalizations, diagnoses made by general practitioners, mortality, and drug dispensing was possible. The majority of studies on anti-osteoporosis drug persistence included a short 1-year follow-up with a focus on first treatment discontinuation. However, determining persistence for the initial drug or first treatment period may result in an underestimation of total exposure. Indeed, this study identified that up to a quarter of patients who discontinued therapy returned to treatment within 1 year of discontinuation which increased to 40% within 5 years. Although it is encouraging that many patients may return to therapy, extended gaps in therapy may result in reduced effectiveness. This may, however, depend on the duration of prior exposure as limited evidence shows a residual anti-fracture effect during posttreatment follow-up that was inversely associated with time on treatment and may be explained by accumulation of bisphosphonates in the bone.[37]

A limitation of this study was that persistence relied on pharmacy dispensing data where the actual intake remained unknown. However, several studies showed that repeated dispensing records are a good indicator of consumptions.[38,39] Second, due to the coding system within general practitioner records, we were not able to disentangle proximal humerus fractures from those of the distal part and shaft. Proximal humerus fractures have been associated with osteoporotic BMD[40,41] and fracture risk,[40] while little is known for those of the shaft and distal part where benefits of treatment with anti-osteoporosis drugs may be less clear. We believe that the impact of this is limited as proximal humerus fractures are the dominant type of humerus fractures after the age of 50 years[42] and the study population was highly likely to have osteoporotic BMD since the Dutch primary care guideline primarily focusses on DXA-diagnosed osteoporosis when considering starting anti-osteoporosis drugs after non-vertebral fractures. Furthermore, this study only identified old age as a significant determinant of discontinuation and the results of several other determinants, including dementia, exposure to DMARDs, initial monthly dosage regime, and alcohol-related diagnoses, should be interpreted with caution due to the low numbers of patients exposed. An incident diagnosis

of renal failure may as well be a determinant of discontinuation but could not be included in the analyses due to the fact that only three patients with this determinant were present. Another limitation was that intravenously administered anti-osteoporosis drugs (zoledronic acid) or subcutaneous drugs (e.g., teriparatide, denosumab) prescribed by a specialist were not (completely) captured as they are either delivered to the patient in the hospital or frequently by special ambulatory pharmacies. A significant underestimation of persistence due to this limitation, however, is unlikely as zoledronic acid was not frequently administered during the study period,[43] denosumab was introduced in the Netherlands in the year 2011, and teriparatide is only reimbursed under restricted conditions.

In conclusion, results identified suboptimal persistence among a cohort of patients with prior fracture, highlighting the need for additional research focused on improving persistence among patients at high risk for subsequent fractures, which includes a better understanding of the underlying reasons for non-persistence. The results of the present study further add to the literature by identifying the frequency of treatment re-initiation following an extended gap and the subsequent persistence with therapy. There are a number of opportunities for improving treatment persistence, including educational interventions targeted at physicians and/or patients as many physicians may be unaware of, and therefore unable to address, non-adherence[44,45] and both physicians as patients may be skeptical or unaware of treatment benefits. Other opportunities include telephone-based counselling,[46] pharmaceutical intervention,[47,48] or use of patient decision aids;[49] yet, few have proven effective in clinical settings.[50] Major target groups for intervention after a recent fracture may be those aged 80 or more years and those restarting therapy following an extended gap.

TABLE S1 | Determinants of non-persistence (> 180-day gap) with anti-osteoporosis drugs after fracture

	Cr. HR (95% CI)	Adj. HR (95% CI)
Gender		
Male	Reference	Reference
Female	0.84 (0.64 – 1.10)	0.89 (0.67 – 1.18)
Age categories		
50 – 59 years	Reference	Reference
60 – 69 years	1.11 (0.76 – 1.64)	1.14 (0.77 – 1.68)
70 – 79 years	1.26 (0.86 – 1.84)	1.25 (0.85 – 1.84)
≥ 80 years	2.00 (1.35 – 2.97)	1.96 (1.30 – 2.95)
Type of index fracture		
Radius/ulna	Reference	Reference
Humerus	0.86 (0.58 – 1.28)	0.81 (0.55 – 1.21)
Clinical vertebral	1.20 (0.91 – 1.57)	1.05 (0.79 – 1.40)
Proximal femur	1.23 (0.91 – 1.66)	1.03 (0.75 – 1.41)
Dosage regime		
Once daily	1.35 (0.93 – 1.98)	1.16 (0.78 – 1.70)
Once weekly	Reference	Reference
Once monthly	0.29 (0.07 – 1.15)	0.29 (0.07 – 1.16)
Drug use [a]		
Systemic glucocorticoids	1.10 (0.73 – 1.66)	1.06 (0.70 – 1.62)
Antidepressants	1.02 (0.71 – 1.47)	1.00 (0.69 – 1.45)
Opioids (tramadol or stronger)	1.11 (0.71 – 1.74)	0.95 (0.60 – 1.52)
Non-steroidal anti-inflammatory drugs	1.00 (0.75 – 1.31)	0.99 (0.75 – 1.32)
Calcium supplements and/or vitamin D	0.94 (0.74 – 1.20)	0.91 (0.72 – 1.16)
Disease-modifying anti-rheumatic drugs	0.72 (0.27 – 1.92)	0.81 (0.30 – 2.19)
Disease occurrence [b]		
Dementia / Alzheimer's Disease	1.64 (0.84 – 3.18)	1.42 (0.73 – 2.79)
Subsequent fractures	1.11 (0.49 – 2.51)	1.07 (0.47 – 2.42)
Upper gastro-intestinal disorders	1.21 (0.54 – 2.72)	1.11 (0.49 – 2.52)
Alcoholism	1.82 (0.94 – 3.53)	1.81 (0.92 – 3.57)

Abbreviations: Cr; crude, Adj; adjusted, HR; Hazard Ratio, 95% CI; 95% Confidence Interval
[a] Reference group is no use within six months prior within that drug category
[b] Reference group is no occurrence within six months prior (ever prior for dementia/Alzheimer's Disease or alcoholism) within that disease category

TABLE S2 | Determinants of non-persistence (> 270-day gap) with anti-osteoporosis drugs after fracture

	Cr. HR (95% CI)	Adj. HR (95% CI)
Gender		
Male	Reference	Reference
Female	0.80 (0.60 – 1.07)	0.86 (0.63 – 1.16)
Age categories		
50 – 59 years	Reference	Reference
60 – 69 years	1.19 (0.78 – 1.83)	1.21 (0.79 – 1.86)
70 – 79 years	1.31 (0.86 – 1.99)	1.31 (0.85 – 2.00)
≥ 80 years	2.19 (1.42 – 3.38)	2.19 (1.40 – 3.43)
Type of index fracture		
Radius/ulna	Reference	Reference
Humerus	0.89 (0.58 – 1.36)	0.82 (0.53 – 1.26)
Clinical vertebral	1.26 (0.94 – 1.69)	1.12 (0.82 – 1.52)
Proximal femur	1.26 (0.91 – 1.75)	1.05 (0.75 – 1.48)
Dosage regime		
Once daily	1.23 (0.81 – 1.87)	1.06 (0.69 – 1.64)
Once weekly	Reference	Reference
Once monthly	0.34 (0.08 – 1.37)	0.34 (0.09 – 1.38)
Drug use [a]		
Systemic glucocorticoids	0.96 (0.60 – 1.53)	0.95 (0.59 – 1.53)
Antidepressants	0.86 (0.57 – 1.31)	0.87 (0.57 – 1.33)
Opioids (tramadol or stronger)	0.89 (0.52 – 1.50)	0.77 (0.45 – 1.32)
Non-steroidal anti-inflammatory drugs	0.98 (0.72 – 1.32)	1.00 (0.74 – 1.36)
Calcium supplements and/or vitamin D	0.91 (0.70 – 1.18)	0.88 (0.68 – 1.15)
Disease-modifying anti-rheumatic drugs	1.04 (0.43 – 2.51)	1.21 (0.49 – 2.95)
Disease occurrence [b]		
Dementia / Alzheimer's Disease	1.48 (0.70 – 3.14)	1.32 (0.61 – 2.82)
Subsequent fractures	0.64 (0.21 – 2.02)	0.63 (0.20 – 1.98)
Upper gastro-intestinal disorders	0.96 (0.36 – 2.60)	0.92 (0.34 – 2.50)
Alcoholism	1.38 (0.61 – 3.10)	1.43 (0.63 – 3.25)

Abbreviations: Cr; crude, Adj; adjusted, HR; Hazard Ratio, 95% CI; 95% Confidence Interval
[a] Reference group is no use within six months prior within that drug category
[b] Reference group is no occurrence within six months prior (ever prior for dementia/Alzheimer's Disease or alcoholism) within that disease category

TABLE S3 | Determinants of non-persistence (> 365-day gap) with anti-osteoporosis drugs after fracture

	Cr. HR (95% CI)	Adj. HR (95% CI)
Gender		
Male	Reference	Reference
Female	0.87 (0.63 – 1.20)	0.94 (0.67 – 1.30)
Age categories		
50 – 59 years	Reference	Reference
60 – 69 years	1.18 (0.75 – 1.85)	1.18 (0.75 – 1.86)
70 – 79 years	1.23 (0.78 – 1.92)	1.22 (0.78 – 1.93)
≥ 80 years	2.32 (1.47 – 3.65)	2.27 (1.42 – 3.64)
Type of index fracture		
Radius/ulna	Reference	Reference
Humerus	0.88 (0.56 – 1.40)	0.83 (0.52 – 1.31)
Clinical vertebral	1.27 (0.92 – 1.74)	1.14 (0.82 – 1.59)
Proximal femur	1.29 (0.91 – 1.82)	1.09 (0.76 – 1.58)
Dosage regime		
Once daily	1.11 (0.70 - 1.78)	0.95 (0.59 – 1.54)
Once weekly	Reference	Reference
Once monthly	0.38 (0.09 – 1.53)	0.37 (0.09 – 1.49)
Drug use [a]		
Systemic glucocorticoids	0.84 (0.50 – 1.42)	0.86 (0.50 – 1.46)
Antidepressants	0.85 (0.54 – 1.33)	0.86 (0.55 – 1.36)
Opioids (tramadol or stronger)	0.99 (0.55 – 1.79)	0.83 (0.47 – 1.47)
Non-steroidal anti-inflammatory drugs	0.92 (0.67 – 1.28)	0.97 (0.70 – 1.35)
Calcium supplements and/or vitamin D	0.86 (0.65 – 1.14)	0.84 (0.63 – 1.11)
Disease-modifying anti-rheumatic drugs	0.48 (0.12 – 1.94)	0.57 (0.14 – 2.33)
Disease occurrence [b]		
Dementia / Alzheimer's Disease	1.68 (0.79 – 3.57)	1.45 (0.67 – 3.11)
Subsequent fractures	0.48 (0.12 – 1.94)	0.47 (0.11 – 1.89)
Upper gastro-intestinal disorders	1.08 (0.40 – 2.92)	1.05 (0.39 – 2.85)
Alcoholism	1.30 (0.54 – 3.17)	1.35 (0.55 – 3.32)

Abbreviations: Cr; crude, Adj; adjusted, HR; Hazard Ratio, 95% CI; 95% Confidence Interval
[a] Reference group is no use within six months prior within that drug category
[b] Reference group is no occurrence within six months prior (ever prior for dementia/Alzheimer's Disease or alcoholism) within that disease category

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CHAPTER 4.3

Increase in prophylaxis of glucocorticoid-induced osteoporosis by pharmacist feedback: a randomised controlled trial

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ABSTRACT

Summary: The aim of this study was to determine whether feedback by pharmacists to prescribers of patients eligible for glucocorticoid-induced osteoporosis prophylaxis would stimulate the prescribing of osteoporosis prophylaxis. The intervention did not significantly increase the prescribing of bisphosphonates in the total study population, but a significant increase was seen in men and in the elderly. However, the proportion of bisphosphonate-treated patients remained low.

Introduction: The aim of this study was to determine whether feedback by pharmacists to prescribers of patients eligible for glucocorticoid-induced osteoporosis prophylaxis (GIOP) would stimulate the implementation of the Dutch GIOP guideline.

Methods: This randomised controlled trial included 695 patients who were dispensed ≥ 675 mg prednisone equivalents without a concomitant bisphosphonate prescription within 6 months before baseline. Pharmacists were asked to contact the physicians of GIOP-eligible patients in the intervention group to suggest osteoporosis prophylaxis. The primary endpoint was a bisphosphonate prescription. Secondary endpoints were a prescription of calcium supplements, vitamin D or any prophylactic osteoporosis drug (bisphosphonate, calcium supplements, vitamin D).

Results: The group assigned to the intervention was slightly younger than the control group (68.7 ± 15.4 vs. 65.9 ± 16.9 years, $p = 0.02$) and used hydrocortisone more often (7.0% vs. 3.1%, $p = 0.02$). Within 6 months, the intervention did not significantly increase the prescribing of bisphosphonates (11.4% after intervention vs. 8.0% for controls; hazard ratio [HR] 1.47, 95% confidence interval [CI] 0.91–2.39). However, subgroup analyses showed a significant increase for the primary endpoint in men (12.8% vs. 5.1%, HR 2.53, 95% CI 1.11–5.74) and patients ≥ 70 years (13.4% vs. 4.9%, HR 2.88, 95% CI 1.33–6.23). The prescribing of calcium and vitamin D was not significantly altered.

Conclusion: This study showed that active identification of patients eligible for GIOP by pharmacists did not significantly increase the prescribing of bisphosphonates in the total study population, but there was an increase in men and the elderly. However, the proportion of GIOP-treated patients remained low.

INTRODUCTION

The use of glucocorticoids, even in low doses, is associated with rapid bone loss and an increased risk of fractures.[1-4] Bisphosphonates have been shown to be the most effective drugs for glucocorticoid-induced osteoporosis prophylaxis (GIOP)[5,6] and are therefore recommended in (inter)national guidelines for management of GIOP.[7-9] The most important recommendation in the Dutch guideline is to consider starting bisphosphonates in post-menopausal women and men over 70 years who are expected to be treated with > 7.5 mg prednisone (equivalents) per day for at least 3 months. In addition, all other patients who are expected to use > 15 mg prednisone (equivalents) for more than 3 months should be treated with bisphosphonates. Although the awareness of the importance of osteoporosis prophylaxis seems to have increased,[10] the widespread implementation of guidelines remains difficult. Audits have shown that only 10–60% of patients who are eligible for GIOP receive appropriate treatment.[11-14] Previous intervention trials that aimed to increase GIOP were mostly conducted by training of physicians (general practitioners and rheumatologists) and frequently included education of patients at risk of GIOP.[15-18] Unfortunately, these attempts have yielded limited success.

Until now, a limited number of studies have determined the impact of pharmacy-based interventions with regard to GIOP.[15,19] In the Dutch health care system, pharmacists share a responsibility with prescribers to properly inform patients on the advantages and disadvantages of pharmacotherapy and to assist physicians in this respect. Therefore, pharmacists could play an important role in the implementation of guidelines for management of GIOP. The previously conducted studies that used a pharmacy-based approach for the improvement of GIOP have shown an increase in the prescribing rates of prophylactic osteoporosis drugs. However, these studies were limited by a lack of randomisation or a lack of power.[15,19] Therefore, the aim of this randomised controlled trial was to determine whether feedback by community pharmacists to physicians of patients eligible for GIOP would stimulate the implementation of the Dutch GIOP guideline.

MATERIALS AND METHODS

STUDY PARTICIPANTS AND SETTING

This randomised controlled trial was conducted at 29 pharmacies from different parts in the Netherlands. Pharmacists were invited to participate in the study by a short announcement in the Dutch Pharmacy Journal. The pharmacies were located all over the Netherlands. There was no particular chain of pharmacies involved.

At each participating pharmacy, drug dispensing data from all patients were collected at baseline (date of first data extraction, January 2005 to May 2005). We selected all patients who were dispensed ≥ 675 mg prednisone equivalents (≥ 67.5 defined daily dosages [DDDs])[7,8] without a concomitant bisphosphonate prescription within the 180 days before baseline and with at least one prescription for a glucocorticoid within the 90 days before baseline. In the Netherlands, the vast majority of the population obtains their medication from only one community pharmacy, enabling the collection of longitudinal medication histories.[20] Medication records of patients were pseudonymised and were sent to the researchers. We have excluded patients who had less than 6 months of medication records before baseline.

INTERVENTION

Block randomisation (using the survey select procedure of SAS, version 8.2) was performed. After the randomisation, the pharmacists received feedback on patients who were assigned to the intervention group. They received a letter with the Dutch GIOP guideline[8] and a list on paper with all the eligible patients. Pharmacists were expected to forward the patients on this list to their own general practitioners and to suggest the start of osteoporosis prophylaxis (a bisphosphonate). It was left at the disposal of the individual pharmacist how to communicate with the general practitioner.

At the end of 6 months of follow-up, additional pharmacy dispensing records of all patients in the intervention and control group (usual care) were retrieved. These medication records were reviewed for the dispensing of bisphosphonates, calcium supplements and vitamin D during the follow-up period. After the study period, pharmacists received comparable information on patients who were originally assigned to the control group.

This study was not covered by the Medical Research Involving Human Subjects Act (WMO) since the patients were not directly exposed to the intervention, and approval by an ethical committee was not required.

OUTCOME MEASUREMENTS

All patients were followed up from baseline until the start of osteoporosis prophylaxis or the end of the study period (the date of second data extraction), whichever came first. The primary endpoint was a dispensing of a bisphosphonate. Secondary endpoints were the dispensing of other prophylactic osteoporosis drugs (calcium supplements or vitamin D) and a dispensing of any prophylactic osteoporosis drug as a composite endpoint (bisphosphonate, calcium supplements or vitamin D, only the first event was counted).

STATISTICAL ANALYSES

We assumed an event rate of 10% in the control group over 6 months and an increase to 20% in the intervention group.[18,21] With a two-sided alpha of 0.05 and 90% power, a total sample size of 584 patients was estimated which was increased to 695 patients.

Chi-square tests or Fisher's exact tests were used to determine baseline differences between the comparison groups for categorical variables and independent sample *t* tests for continuous variables ($p < 0.05$). Cox proportional hazard models were used to estimate hazard ratios (HRs) for the start of osteoporosis prophylaxis during the follow-up period by comparing the intervention group to the control group. Hazard ratios were adjusted for covariates that were unevenly distributed between the intervention group and control group ($p < 0.05$). Patients who did not receive any prescription of glucocorticoids during the follow-up period were censored at 1 day after baseline.

In subgroup analyses, results were stratified by gender, the number of prednisone equivalents (DDDs) received in the 6 months before baseline (67.5–134, 135–270, > 270) and age categories (≤ 70, > 70 years) for the primary and composite endpoint.

Finally, a Kaplan–Meier plot was used to visualize the time to start of bisphosphonate use after baseline and the proportion of patients being newly treated for GIOP during the study period. This plot was stratified by the randomised intervention. All analyses were performed using SAS, version 9.1.

RESULTS

During the first data extraction period, 735 patients were selected from the participating pharmacies. Of these patients, 31 (4.2%) were not eligible for bisphosphonate prophylaxis according to the Dutch guideline. These patients were either females younger than 50 years or males younger than 70 years using less than 1 350 mg (135 DDDs) prednisone equivalents, or females older than 50 or males older than 70 using less than 675 mg (67.5 DDDs) prednisone equivalents. Moreover, nine patients (1.2%) were excluded as they had medication records available for less than 6 months prior to the first extraction date. Overall, 695 patients could be randomised, with 343 allocated to the intervention group and 352 to the control group. During the follow-up period, 38 (11.1%) patients who were allocated to the intervention group and 36 (10.2%) patients in the control group did not receive any new glucocorticoid prescription but did collect prescriptions for other drugs. Furthermore, 63 (18.4%) patients in the intervention group and 72 (20.5%) patients in the control group did not collect any prescription during follow-up (Figure 1).

The group assigned to the intervention was slightly younger than the control group (65.9 ± 16.9 vs. 68.7 ± 15.4 years, $p = 0.02$) and used hydrocortisone more often in the 6 months before baseline (7.0% vs. 3.1%, $p = 0.02$). All other baseline characteristics and mean follow-up time were similar between the intervention and the control group (Table 1).

TABLE 1 | Baseline characteristics of patients in the intervention group and control group

	Control group N = 352	Intervention group N = 343	P-value
Follow-up (mean ± SD months)	6.2 ± 1.1	6.2 ± 1.1	NS
Female, n (%)	55.4	54.5	NS
Age (mean ± SD years)	68.7 ± 15.4	65.9 ± 16.9	0.02
Age categories, n (%)			
< 50 years	11.6	18.4	0.01
50 – 70 years	36.1	31.5	NS
> 70 years	52.3	50.1	NS
Type of glucocorticoid in the 6 months before baseline, n (%) [a]			
Betamethasone	1.4	0.3	NS
Cortisone acetate	3.1	4.4	NS
Dexamethasone	7.9	6.1	NS
Fludrocortisone	2.0	2.9	NS
Hydrocortisone	3.1	7.0	0.02
Methylprednisolone	0.3	0.3	NS
Prednisolone	17.2	17.2	NS
Prednisone	79.3	75.5	NS
Triamcinolone	1.7	1.5	NS
Cumulative DDDs of prednisolone equivalents in the 6 months prior to baseline (mean ± SD)	183.3 ± 161.4	185.0 ± 172.3	NS
Cumulative DDD categories, n (%)			
< 135 DDDs	41.2	37.9	NS
135 – 270 DDDs	44.6	50.7	NS
> 270 DDDs	14.2	11.4	NS
Co-medication in the 6 months prior to baseline, n (%)			
Opioid analgesics	6.2	7.0	NS
Cytostatic drugs	5.7	3.8	NS
Anti-emetic drugs	4.5	2.9	NS
Calcium	16.7	16.6	NS
Vitamin D	6.0	7.0	NS
HRT or SERMs	0.9	2.0	NS
Anti-ulcer drugs	43.6	44.3	NS
Bisphosphonate use > 6 months prior to baseline	12.2	10.8	NS

Abbreviations: HRT; hormone replacement therapy, SERM; selective oestrogen receptor modulator, SD; standard deviation, DDD; Defined Daily Dosage. Comparison of baseline characteristics between groups was significant at $p < 0.05$. [a] Use of more than one type of glucocorticoids per patient is possible.

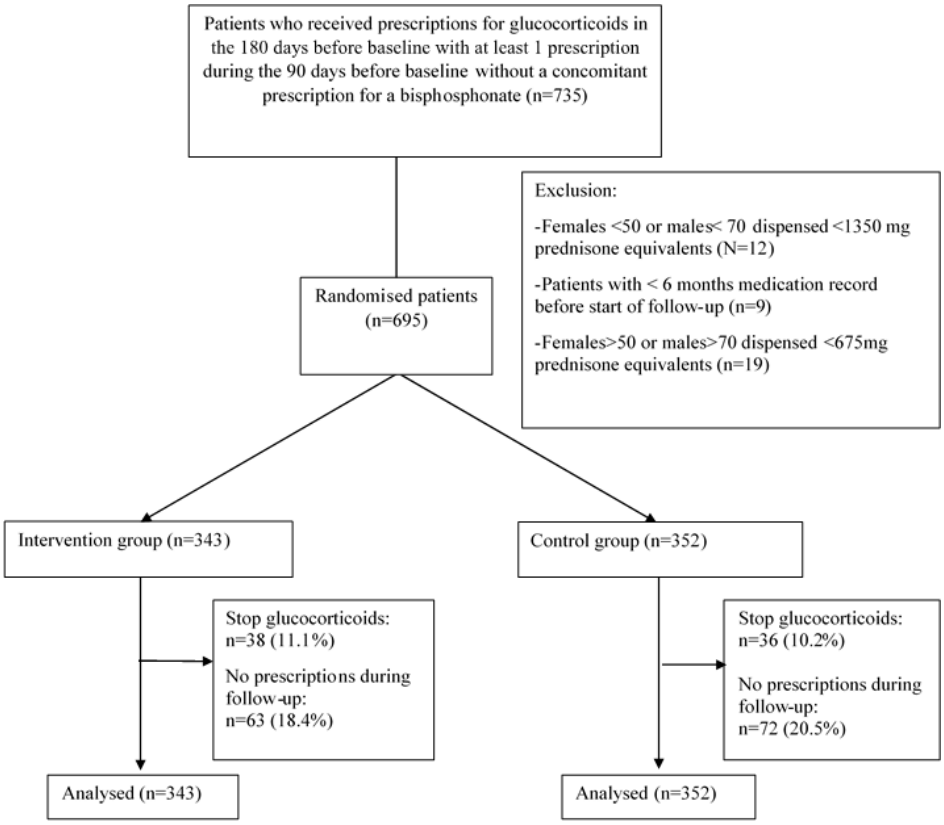

FIGURE 1 | Flow-chart of the study procedure

During a mean follow-up period of 6.2 months, the primary endpoint (a prescription for a bisphosphonate during follow-up) was achieved by 39 patients (11.4%) in the intervention group and by 28 patients (8.0%) in the control group. Figure 2 shows the time to initiation of a bisphosphonate for both study groups. The intervention did not significantly increase the prescribing rate of bisphosphonates when compared to the control group (unadjusted HR 1.47, 95% confidence interval [CI] 0.91–2.39). This effect changed marginally after adjustment for age and use of hydrocortisone in the 6 months before baseline (Table 2). However, subgroup analyses showed that the prescribing rate of bisphosphonates was significantly increased in the intervention group for male patients (12.8% vs. 5.1%; unadjusted HR 2.53, 95% CI 1.11–5.74; adjusted HR 2.55, 95% CI 1.12–5.80) and for patients older than 70 years (13.4% vs. 4.9%; unadjusted HR 2.88, 95% CI 1.33–6.23; adjusted HR 2.99, 95% CI 1.38–6.47). The received cumulative number of DDD prednisone equivalents in the 6 months before baseline did not change the effect of the intervention. Similar results were seen for the composite endpoint of any prophylactic osteoporosis drug (Table 3).

TABLE 2 | Start of osteoporosis prophylaxis drugs after intervention, as compared to usual care

Treatment	Start OP intervention (%)	Start OP control (%)	Unadjusted HR [95% CI]	Adjusted HR [95% CI] [a]
Bisphosphonate	11.4	8.0	1.47 [0.91 – 2.39]	1.54 [0.95 – 2.50]
Calcium	5.3	2.6	2.06 [0.93 – 4.59]	2.12 [0.95 – 4.72]
Vitamin D	3.5	1.7	2.05 [0.77 – 5.47]	2.08 [0.78 – 5.55]
Bisphosphonate, calcium or vitamin D	13.4	9.4	1.48 [0.94 – 2.31]	1.53 [0.98 – 2.39]

Abbreviations: OP; osteoporosis prophylaxis drugs, HR; hazard ratio, CI; confidence interval
[a] Adjusted for age categories (≤ 70, > 70) and use of hydrocortisone in the 6 months before baseline

TABLE 3 | Start of osteoporosis prophylaxis drugs after intervention, as compared to usual care, stratified by gender, cumulative dosage prednisone equivalents and age categories

	Start OP intervention (%)	Start OP control (%)	Unadjusted HR [95% CI]	Adjusted HR [95% CI] [a]
Bisphosphonate				
Overall	11.4	8.0	1.47 [0.91 – 2.39]	1.54 [0.95 – 2.50]
Stratified by gender				
Men	12.8	5.1	2.53 [1.11 – 5.74]	2.55 [1.12 – 5.80]
Women	10.2	10.3	1.03 [0.55 – 1.93]	1.10 [0.58 – 2.06]
Stratified by cumulative dosage prednisolone equivalents within 6 months before baseline				
67.5 – 134 DDDs	10.8	7.6	1.52 [0.69 – 3.36]	1.54 [0.70 – 3.38]
135 – 270 DDDs	10.9	6.4	1.65 [0.77 – 3.56]	1.67 [0.77 – 3.59]
> 270 DDDs	15.4	14.0	1.48 [0.50 – 4.41]	1.47 [0.49 – 4.38]
Stratified by age category [b]				
≤ 70 years	9.4	11.3	0.84 [0.43 – 1.63]	0.89 [0.46 – 1.73]
> 70 years	13.4	4.9	2.88 [1.33 – 6.23]	2.99 [1.38 – 6.47]
Bisphosphonate, calcium or vitamin D				
Overall	13.4	9.4	1.48 [0.94 – 2.31]	1.53 [0.98 – 2.39]
Stratified by gender				
Men	14.7	6.4	2.33 [1.11 – 4.89]	2.32 [1.10 – 4.88]
Women	12.3	11.8	1.09 [0.61 – 1.93]	1.14 [0.64 – 2.04]
Stratified by cumulative dosage prednisolone equivalents within 6 months before baseline				
67.5 – 134 DDDs	11.5	9.0	1.38 [0.66 – 2.89]	1.39 [0.66 – 2.93]
135 – 270 DDDs	13.8	8.3	1.61 [0.82 – 3.15]	1.60 [0.81 – 3.15]
> 270 DDDs	17.9	14.0	1.77 [0.62 – 5.05]	1.74 [0.61 – 4.99]
Stratified by age category [b]				
≤ 70 years	13.5	12.5	1.10 [0.61 – 1.98]	1.16 [0.64 – 2.09]
> 70 years	13.4	6.5	2.14 [1.07 – 4.30]	2.22 [1.11 – 4.47]

Abbreviations: OP; osteoporosis prophylaxis drugs, HR; hazard ratio, CI; confidence interval, DDDs; defined daily dosage prednisolone equivalents
[a] Adjusted for age categories (≤ 70, > 70) and use of hydrocortisone in the 6 months before baseline
[b] Adjusted for hydrocortisone use in the 6 months before baseline

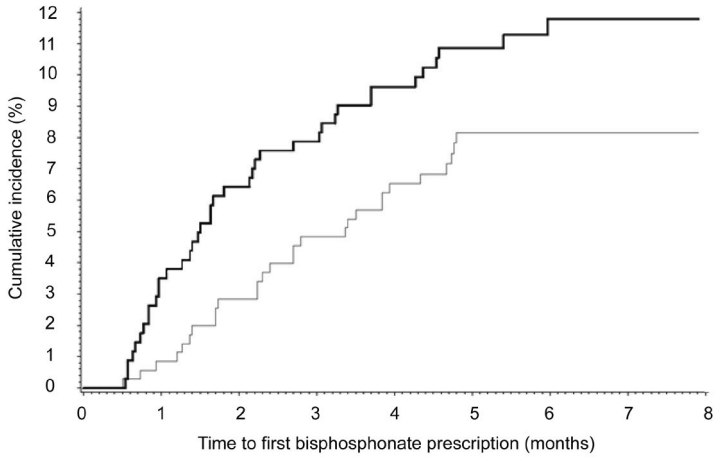

FIGURE 2 | Incidence bisphosphonate use in the intervention group (black line) and control group (grey line)

DISCUSSION

This randomised controlled trial showed that active identification of GIOP-eligible patients by community pharmacists did not significantly increase the prescribing rate of bisphosphonates in the total study population. However, subgroup analyses showed that there was a significant increase in the primary endpoint in males and in the elderly (> 70 years). Similar results were seen for the composite endpoint of any prophylactic osteoporosis drug (bisphosphonate, calcium, or vitamin D).

To the best of our knowledge, this is the first randomised controlled trial where pharmacists identified GIOP-eligible patients and subsequently contacted the prescriber, without further training of the patient or the physician.[22] The only previously conducted pharmacy-based randomised controlled trial that aimed to increase GIOP found an increased prescribing rate of calcium but not of bisphosphonates.[19] This trial was conducted at 15 community pharmacies (intervention 70 patients, control 26 patients). The pharmacists received training for GIOP, identified eligible patients, gave them education for GIOP and contacted the prescriber when necessary. However, pharmacists in both the intervention and control groups received training about GIOP and the importance of bone mineral density (BMD) testing which may have diluted the results. Another randomised controlled trial has shown a twofold increase (28 patients (22%) intervention group vs. 14 patients (11%) control group; relative risk 2.1, 95% CI 1.1–3.7) in the composite endpoint of BMD testing or incident osteoporosis treatment with a community pharmacist screening programme.[21] In contrast to the present study, all patients and pharmacists received education about osteoporosis. Other attempts to increase GIOP mostly included educational interventions directed at physicians (general practitioners or rheumatologists) but were often without or with modest results.[16-18]

The lack of an overall intervention effect was accompanied by a low number of bisphosphonate-treated patients.[14,17] It should be noted that the study population did not include patients who already received a prescription for a bisphosphonate in the 6 months prior to baseline. Chitre et al. (2008) similarly excluded these patients and found comparable incident treatment rates for osteoporosis prophylaxis. In addition, our study population included patients who received a bisphosphonate more than 6 months before baseline (10.8% in the intervention group, 12.2% in the control group). These patients could have had earlier adverse effects for bisphosphonates or had other reasons for discontinuing these drugs. Moreover, not all patients still used glucocorticoids during follow-up or tapered off the dose, and as a result, GIOP prophylaxis was no longer required.

In the control group, the proportion of GIOP-treated males was twofold lower as compared to females. The neglecting of osteoporosis prophylaxis in males is in line with other studies.[11,14,23] The difference in the intervention effect between males and females may be explained by this phenomenon; prescribers may have been more likely to have previously considered osteoporosis prophylaxis in females. The low prescribing rate in the elderly may be explained by the initial belief of physicians that extra treatment with bisphosphonates would be inappropriate due to the presence of multiple co-morbidities or a large number of medicines. On the other hand, elderly patients do have a higher absolute fracture risk and the consequences of fractures (especially for those of the hip) can be tremendous.[24] The increased prescribing of bisphosphonates for elderly in the intervention group may be explained by an increased awareness for this fact. It should, however, be noted that the power of this study was not calculated specifically for these subgroup analyses.

Strengths of this study include its size and the simple set-up of the intervention. In contrast to previous trials, patients and physicians were not educated for GIOP and pharmacists only received the recent guideline without further training.[19,21] This study is therefore a better reflection of the real-life situation. The identification of patients at risk for GIOP can easily be integrated in the tasks of the pharmacists and is not labour intensive or costly when compared to interventions involving education of physicians and/or patients.[25] However, the lack of an overall significant increase in the number of bisphosphonate-treated patients calls for additional measures. The intervention in its present from can be combined with interdisciplinary meetings between pharmacists and general practitioners beforehand and after follow-up, which include feedback about current prescribing and differences between practices. This approach is not very costly and is achievable in daily practice. In addition, clinical rules are currently implemented, and this would make it even easier to extract GIOP-eligible patients from pharmacy information systems. Indeed, a large randomised controlled trial (RCT) showed the significant benefit of a more intensive, pharmacist-led intervention in reducing the number of prescribing errors.[26] Pharmacists did not only give feedback to physicians about medication errors during meetings, but also reviewed medical records and invited the patients.

The major limitation of this study is that we do not know how motivated the pharmacists were to perform the intervention. It is likely that pharmacists did not notify all GPs, but this has not been systematically registered. In addition, we do not know if discussions between prescribers and their patients about the start of GIOP took place. Possibly, a number of approached patients refused to start osteoporosis prophylaxis. Therefore, the actual effect of the pharmacist intervention on the physician's behavior may have been greater than the reported effect. In addition, we had no clinical data available such as (prior) BMD testing or the occurrence of fractures (history). Guidelines recommend that pre-menopausal women who use 7.5–15 mg of prednisone equivalents for ≥ 3 months should receive a BMD measurement. However, this study presumably included post-menopausal women (≥ 50 years). Furthermore, we also have included patients who were dispensed less than 135 DDD prednisone equivalents in the 6 months before baseline (41.2% in the control group, 37.9% in the intervention group), who were possibly not eligible for GIOP according to the Dutch guideline. However, in the Netherlands, patients are frequently dispensed medication for 3 months, and we would have missed these patients if the inclusion period was only 3 months before baseline. Moreover, all patients were required to receive a dispensing for glucocorticoids within 3 months before baseline, and our results show that the cumulative number of DDD prednisone equivalents did not modify the intervention effect. Another limitation of this study was that we were unable to exclude patients where osteoporosis prophylaxis would have been contraindicated or inappropriate (e.g. patients with serious cognitive or renal impairment). Finally, this was a non-blinded RCT with a lack of clinical equipoise between the pharmacists in the intervention group.[27] In other words, it is very likely that all included pharmacists saw the importance of the intervention. As a result, pharmacists could have been motivated to self-identify patients other than those in the intervention group who would also benefit from GIOP. This may have masked the effect of the intervention.

The present study showed that simple feedback by community pharmacists to physicians about patients eligible for GIOP did not manage to significantly increase the prescribing of bisphosphonates in the overall study population. Subgroup analyses showed a significant increase in males and in patients older than 70 years. However, the absolute number of GIOP-treated patients remained low which calls for more intensive pharmacy-based interventions.

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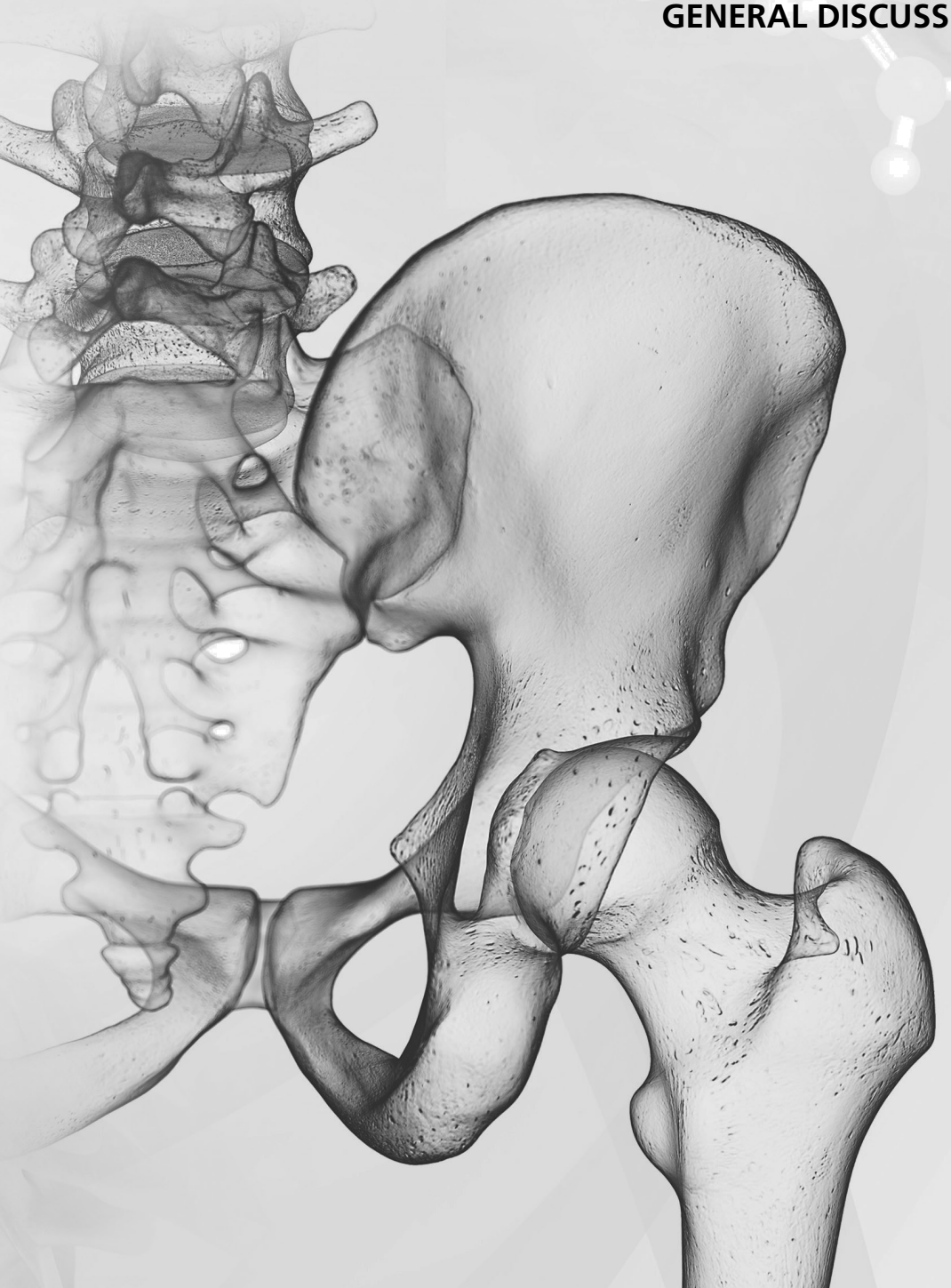
CHAPTER 5

GENERAL DISCUSSION



The overall thesis aim was to evaluate and to help improve prediction of absolute fracture risk and the implementation of pharmacological treatment. In the first section of this discussion we will discuss the clinical utility of fracture risk prediction models including differences between the available models, the external validity of the most used prediction model FRAX along with a discussion on the impact of the study design on development and evaluation of prediction models. Furthermore we will discuss the evidence for anti-fracture efficacy of anti-osteoporosis drugs (AODs) on the basis of FRAX-predicted fracture risk. The second section of this discussion will discuss the barriers and potential measures to improve the implementation of pharmacological treatment among high-risk individuals. Following from this discussion we will conclude with clinical and methodological recommendations.

THE UTILITY OF FRACTURE RISK PREDICTION MODELS

The utility of fracture risk prediction models is multifactorial. They may be used for primary prevention by targeting pharmacological treatment to those at high-risk by opportunistic case-finding or by population-based screening depending on the cost-effectiveness of the latter approach. They may also serve as a risk-communication tool where the physician and patient can discuss the absolute fracture risk worthwhile to intervene. Another application is for risk stratification in randomized clinical trials as has been advocated in guidance from the Committee for Medicinal Products for Human Use (CHMP) for the assessment of anti-osteoporosis drug efficacy.[1]

Although these are different applications, they share the necessity of the prediction model to have adequate predictive performance. Unfortunately, many prediction models have been developed while very few have been actually validated in an external population. Until now, three of the 46 prediction models for fracture risk have been evaluated more than once outside of the development populations.[2] These include GARVAN,[3] QFracture[4,5] and the World Health Organization (WHO) FRAX model.[6] Although these models all predict absolute fracture risk, they differ considerably in the extension of the external validation but also in the included risk factors, the data source used for development, methods used for expressing absolute risk, the types of fractures included in the outcome definition, and the time frame over which absolute risk is predicted. These differences are shown in Table 1. In contrast to GARVAN and Qfracture, FRAX adjusts fracture risk for mortality risk and can be applied to every country when country-specific data for fracture and mortality incidence are provided.[6]

EXTERNAL VALIDITY AND UPDATING OF FRAX

Key aspects for validity of a prediction model are discrimination and calibration.[7] A prediction model adequately discriminates risk when predicted risk is higher among those who get the outcome of interest as compared to those who do not. Calibration refers to the agreement

of predicted risk with the actual observed risk. The latter is particularly important when thresholds for absolute risk are used for clinical decision making, which has been advocated for FRAX in e.g. the UK[8] and in the USA.[9] Any miscalibration may then influence the decision to treat or not to treat.

In our external validation study of the UK version of FRAX (Chapter 2.2) in the UK Clinical Practice Research Datalink (CPRD), we found that in the general community-dwelling population discrimination was good for the 10-year risk of hip fracture and moderate for the 10-year risk of major osteoporotic fracture (MOF), which is in line with other external validation studies.[2] We also showed that UK FRAX significantly over-predicted the 10-year risk of MOF and hip fracture when fractures were extracted from primary care records from CPRD.

TABLE 1 | Overview of content, applicability, development, and validation characteristics of fracture risk prediction models

	FRAX	Qfracture	GARVAN
Content			
	Age (40 – 90 years)	Age (30 – 85 years)	Age (60 – 96 years)
	Sex (male/female)	Separate models for males and females	Sex (male/female)
	Body mass index (continuous)	Body mass index (continuous)	-
	Previous fracture at any site (yes/no)	-	Previous fracture at any site (0, 1, 2, 3+) after the age of 50
	Parental history of hip fracture (yes/no)	Parental history of osteoporosis (yes/no)	
	Currently smoking (yes/no)	Smoking status (non-smoker, former smoker, light smoker [<10 cigarettes/day], moderate smoker [10-19 cigarettes/day], heavy smoker [≥20 cigarettes/day])	
	Alcohol consumption of ≥ 3 units/day (yes/no)	Alcohol consumption (none, trivial < 1unit/day, light 1 – 2 units/day, medium 3-6 units/day, heavy 7-9 units/day, very heavy > 9 units/day)	
	Secondary osteoporosis (type 1 diabetes mellitus, osteogenesis imperfecta, hyperthyroidism, hypogonadism, premature menopause, malnutrition, malabsorption, chronic liver disease; yes/no)		
	Rheumatoid arthritis (yes/no)	Rheumatoid arthritis (yes/no)	
	Oral glucocorticoids (yes/no)	Oral glucocorticoids (yes/no)	
	Bone mineral density (T-score or BMD [g/cm^2] of the femoral neck, optional)		Bone mineral density (T-score or BMD [g/cm^2], optional)

		History of falls (yes/no)	Number of prior falls in the 12 months prior (0, 1, 2, 3+)
		Diagnosis of cardiovascular disease (yes/no)	
		Diagnosis of type 2 diabetes (yes/no)	
		Diagnosis of asthma (yes/no)	
		Use of tricyclic antidepressants (yes/no)	
		Diagnosis of chronic liver disease (yes/no)	
		Diagnosis of gastrointestinal malabsorption (yes/no)	
		Diagnosis of other endocrine symptoms (yes/no)	
		Hormone replacement therapy (yes/no)	
		Menopausal symptoms (yes/no)	
Applicability			
Prediction interval	10 years	1, 2, …10 years	5, 10 years
Outcome definition	Hip fracture, major osteoporotic fracture (first of hip, clinical spine, forearm, humerus)	Hip fracture, major osteoporotic fracture (first of hip, clinical spine, forearm)	Hip fracture, any osteoporotic / fragility fracture
Mortality adjusted	Yes	No	No
Countries	57	UK only	3
Inclusion in guidelines	Yes	Yes	Yes
Development[2]			
Population basis, N	46 340	2 404 235	2216
Population basis, countries	9	UK only	Australia
Study type	Prospective cohorts	Retrospective cohort	Prospective cohort
Validation[2]			
Independent validation	Yes	Yes	Yes
Number of validation studies	26	3	6
Population basis, N	4 624 438	3 485 952	229 162
Population basis, countries	9	UK only	3

To date, calibration of FRAX has been evaluated in five independent cohorts from five countries.[10] Three of them have reported suboptimal calibration which included a study in the UK. In line with our results, this study showed an over-prediction of UK FRAX for risk of hip fracture in the general population.[4] It was performed in the UK QResearch database where hip fractures were extracted from primary care data. A key finding from our study, however, was that extraction of hip fractures from hospitalization data instead of primary care records changed the conclusion where we found good calibration of UK FRAX for the 10-year risk of hip fracture in the general population.

Another issue that may influence calibration of FRAX for MOF risk is the frequently used imputation of incidence for this outcome. This method assumes equal age-and-sex-specific

incidence rate ratios for hip fracture relative to MOF as observed in Sweden over the period 1987-1996, and has been used for calibration of the Dutch FRAX model[11] We found observed MOF incidence to be significantly higher than expected based on the imputation method among women over a wide age-range, where fractures were extracted from both primary care and hospitalization records in the Dutch PHARMO database network (Chapter 2.1). This finding is in line with the few studies that have addressed this issue.[12-14] A possible explanation, apart from a difference in geographical region, is a secular change in fracture incidence where the drop in MOF incidence proceeded more slowly than for hip fracture. This is supported by the few studies that have assessed trends in (non-hip) fracture incidence.[15,16]

Furthermore, we showed that UK FRAX significantly over-predicted the 10-year risk of hip fracture and MOF in individuals with rheumatoid arthritis (RA) in CPRD (Chapter 2.2), which diminished but remained significant for the 10-year risk of hip fracture upon linkage to hospitalizations. Because FRAX incorporates population-based mortality rates, one possible explanation for the over-prediction of UK FRAX in RA is higher competing mortality risk as compared to the general population.[17,18] Treatment with disease-modifying anti-rheumatic drugs (DMARDs) and biologics may also have influenced observed fracture risks since these drugs have been associated with a protective effect on loss of BMD and a reduced risk of fracture, but evidence has been conflicting.[19] AOD treatment during follow-up could also have lowered observed risks, but even when we increased the average observed risk by 50% among those who did receive AOD treatment (assuming a 50% risk reduction with AOD treatment) over-prediction remained.

We also found that in patients with a recent hip fracture, most risk factors as in FRAX were also risk factors for a subsequent (non-hip) fracture in the year thereafter (Chapter 3.1). The most important risk factors were female gender, a prior fracture, and secondary osteoporosis. However, increasing age, current smoking, a record of alcohol use, and rheumatoid arthritis turned out to be no statistically significant risk factors. In our study, subsequent non-hip fractures in the year after hip fracture were extracted from CPRD, where just under 10% of the study population was transferred out of the database. Differential loss-to-follow-up between age categories may explain this finding for age.

Furthermore, we showed that the extension of FRAX predictors with glucocorticoid dose and psychotropic drugs did not increase predictive performance for the 10-year risk of hip fracture on the population-level (Net Reclassification Improvement [NRI] of 0.01), where hip fractures were extracted from hospitalizations (Chapter 2.3). Among RA patients, high-dose glucocorticoids, duration of RA disease and secondary osteoporosis were associated with hip fracture risk independent of predicted FRAX risk, but addition of these variables to the recalibrated UK FRAX algorithm did not increase the predictive performance (NRI of 0.01). Also here, hip fractures were extracted from hospitalizations.

IMPACT OF THE STUDY DESIGN ON PREDICTIVE MODELLING

There are several important aspects that relate to the study design that should be considered in the interpretation of results from studies that develop, externally validate or update prediction models, including our studies regarding the FRAX algorithm. These are outlined and discussed in this paragraph.

Information bias is a key source of error in predictive modelling. In this thesis, we showed that hip fractures were under recorded in primary care records when compared to hospitalization data which results in misclassification of the outcome (Chapters 2.2 and 2.3). A major cause for this discrepancy may be the high rate of institutionalization following hip fracture and this event may be subsequently missed by the primary care physician. In addition, also in the case of non-hip fractures, primary care physicians may not register a fracture that was subsequently diagnosed in the hospital, or patients may go directly to the emergency department. It remains therefore uncertain how well UK FRAX calibrated for MOF risk in our study (Chapter 2.2). Interestingly, another model that predicts the risk of hip fracture and MOF, Qfracture, has been developed in the UK primary care database Q-research and has been externally validated in other UK primary care databases including CPRD and THIN with excellent discrimination and calibration.[5,20] Our results, however, suggest that predicted risks from Qfracture should be interpreted with caution where predicted risks may be an underestimate of the true risk.

In addition, misclassification of the outcome may change over time. In Chapter 3.1 we showed a significant increase in the one-year risk of subsequent non-hip fracture (as recorded in primary care records from CPRD) after hip fracture over the period 2000 – 2010 which remained significant after adjustment for major risk factors for fracture. This might have been caused by improved survival after hip fracture as is shown in Chapter 3.2, but it may also relate to improvements in record keeping by primary care physicians although we were not able to confirm this hypothesis yet.

The nature of the data source may also influence the incidence of the outcome. In Table 2 we compare incidence rates of hip fracture between the PHARMO database network (Chapter 2.1), the Dutch National Hospitalization Registry (NHR)[11] and the Dutch claims database VEKTIS.[21] Although the differences in calendar year periods make a direct comparison difficult, there are some fundamental differences between the data sources that may influence incidence rates. Both NHR and VEKTIS comprise of the total population of the Netherlands while the PHARMO Database Network is a dynamic cohort that contains a part of the Dutch community-dwelling population. Indeed, the incidence of hip fracture has been reported to be 2 to 20-fold higher in institutionalized patients[22,23] depending on age and sex. Another difference between NHR/VEKTIS and the PHARMO Database Network is that the latter links records by means of a probability algorithm. Record linkages may be incomplete due to the probability algorithm, and an increased number of registries to link with PHARMO (pharmacy data to NHR, mortality

register, primary care data) may lead to an increased number of patients that cannot be linked – and therefore reduced incidence rates. This probability linkage is different compared to linkage by a social security number or a health insurance number. In addition, the "backbone" of linkage in PHARMO is pharmacy data, rather than e.g. the NHR. Furthermore, the higher incidence between VEKTIS and the NHR can be explained by a different definition for incidence. The NHR study excluded individuals with a prior hip fracture in the 5 years before, and counted a hip fracture in the same year only once.[11] The VEKTIS study counted all hip fractures in the year 2010, aggregated by sex and age category, regardless of fracture history or subsequent fracture status.[21]

TABLE 2 | Age-and-sex-specific incidence rates of hip fracture in the Netherlands, by data source

	PHARMO Database Network	NHR	VEKTIS
Year period	2002 – 2011	2004 – 2005	2010
Women, by age category	IR (95% CI)	IR	IR
50 – 54	2.1 (1.4 – 2.8)	2.1	4.9
55 – 59	3.0 (2.1 – 3.8)	4.2	9.0
60 – 64	6.7 (5.4 – 8.1)	8.1	13.1
65 – 69	9.3 (7.5 – 11.1)	15.3	20.0
70 – 74	19.3 (16.5 – 22.1)	28.6	36.7
75 – 79	35.6 (31.2 – 40.0)	53.6	74.3
80 – 84	72.3 (64.5 – 80.1)	100.5	127.5
85 – 89	116.5 (102.4 – 130.6)	188.2	- *

Abbreviations; NHR; Dutch National Hospitalization Registry, IR: incidence rate per 10,000 person years in PHARMO Database Network and incidence rate per 10,000 persons in NHR and VEKTIS, 95% CI: Confidence Interval. * IRs were reported for the aggregated age-category of 85+ years

Another issue is selection bias. In Chapters 2.2 and 2.3 we have excluded individuals who ever received anti-osteoporosis drugs before the index date from the study population. This may have resulted in a population with lower fracture risk. However, the developmental cohorts of FRAX also excluded individuals who ever received anti-osteoporosis drug treatment, and therefore our method was in line with FRAX.

With regard to statistical methods for obtaining predicted and observed (fracture) risks in the presence of a competing (mortality) risk, regular Cox regression or Kaplan-Meier life-table analysis produces biased estimates. Instead, we advocate Fine and Gray regression analysis and the cumulative incidence function where censoring due to the competing risk is treated as informative.[24] Furthermore, we have applied the Net Reclassification Improvement for determining the added predictive value of new risk factors[25] to the FRAX model (Chapter 2.2) or to FRAX predictors (Chapter 2.3). An advantage of the NRI is that it evaluates the potential of a new predictor to change individual patients' risk strata and therefore to alter treatment decisions. A limitation, however, is that reclassification of fracture cases to a higher

risk category has an equal weight in the calculation than reclassification of non-cases to a higher risk category, and vice versa. In addition, the NRI result depends on the intervention threshold that was used and therefore not necessarily applies to situations where different thresholds are incorporated.

EFFICACY OF ANTI-OSTEOPOROSIS DRUGS AMONG THOSE AT HIGH FRAX-PREDICTED FRACTURE RISK

The interaction between FRAX-predicted absolute fracture risk and the anti-fracture efficacy of several anti-osteoporosis drugs (AODs) has been studied in a series of post-hoc analyses from randomized controlled trials. Relative fracture risk reduction was greater with increasing FRAX-based 10-year risk of MOF or hip fracture for exposure to denosumab, bazedoxifene, and clodronate, while treatment with raloxifene, strontium ranelate, alendronate and teriparatide resulted in stable and significant anti-fracture efficacy over the total range of FRAX-based probabilities (but with a greater absolute risk reduction among those at higher risk).[26-28] There are several possible explanations for this heterogeneity in results. First, the lack of an interaction between the efficacy of anti-fracture drugs and FRAX-based probabilities might relate to the relative absence of low risk subjects and therefore an inability to detect any attenuation of efficacy with low fracture probabilities. Second, biochemical and structural properties of anti-osteoporosis drugs may potentially contribute to the difference between the drug classes which all influence bone mineral density but by which the physiologic pathways differ. However, even within drug classes there is disparity in treatment efficacy with increasing FRAX risk; including the selective estrogen receptor inhibitors (SERMs) bazedoxifene and raloxifene, and the bisphosphonates alendronate and clodronate. In the case of SERMs, differences in study design or analysis cannot contribute to this finding since these findings arose from a single study with data from the same RCT.[29]

The studies that have assessed the efficacy of AODs in general and across FRAX-based absolute risk categories, have predominantly included a population that was selected on the basis of low (osteoporotic) BMD or a prior fracture. This leaves room for speculation about the anti-fracture efficacy of AODs among individuals selected at high-risk without information on BMD where individuals with normal or osteopenic BMD may be selected. To date, one RCT has randomly recruited individuals from primary care lists irrespective of BMD (3974 women ≥ 75 years) to demonstrate anti-fracture efficacy of clodronate.[30] The anti-fracture efficacy became greater with increasing FRAX-predicted risk without information on BMD. Furthermore, several studies have shown that BMD falls progressively with increasing FRAX-predicted risk which was observed in BMD referral populations[31,32] but also in studies that were conducted in the general community-dwelling population.[33,34] Furthermore, for risedronate, a post-hoc analysis of four trials among women with osteopenia without history of vertebral fractures (BMD T-score -2.5 to -1.0) showed a significant reduction in risk of vertebral and non-vertebral fractures of 73%.[35] Still, preplanned randomized clinical trials are warranted

to provide further evidence for anti-fracture efficacy of anti-osteoporosis drugs among those with osteopenic BMD and with high fracture risk on the basis of FRAX. Currently, two large pragmatic RCTs are running (SCOOP in the UK, and SALT in the Netherlands) that will shed more light on the effectiveness of anti-osteoporosis drugs in clinical practice among patients selected on the basis of a screening-program based on absolute FRAX-predicted fracture risk among women with BMD T-score ≤ -2[36] and among women regardless of BMD T-score.[37]

PHARMACOLOGICAL CARE GAP AMONG INDIVIDUALS AT HIGH FRACTURE RISK

In this thesis we show a substantial care gap for the pharmacological prevention of fracture risk amongst two high-risk groups; those with a recent fracture (secondary fracture prevention) and those eligible for prevention of glucocorticoid-induced osteoporosis (GIOP). Amongst hip fracture patients, who have shown to significantly benefit from AOD treatment irrespective of BMD,[38] the overall treatment rates remained far from adequate in the year 2010, despite considerable improvement over that decade, with just under 50% of patients not receiving AOD treatment within the subsequent year (Chapter 4.1). Males in particular were at increased risk of not receiving drug treatment throughout the study period, which is well in line with previous literature. In addition, we show that the prescribing of bisphosphonates in those eligible for GIOP was very low over a period of six months (8%) (Chapter 4.3), despite the availability of national guidance. We also show that, when AODs were initiated within one year after a major osteoporotic fracture, 25% stopped treatment within one year which increased to 55% within five years (Chapter 4.2). The only risk factor was old age where the elderly (> 80 years) had higher risk for early discontinuation.

There may be several reasons for this pharmacological care gap. First, it may involve beliefs and appraisal of both physicians and patients for fracture prevention. They may assign fracture risk prevention as low priority and dismiss the occurrence of a fragility fracture or high fracture risk as a problem linked to ageing rather than an opportunity for treatment. This may result from a lack of awareness about the consequences in terms of significant decline in quality of life and where we have shown that one in five hip fracture patients will have died in the first year, which even increases to 30% to 44% among elderly males (Chapter 3.2). In addition, we have shown that approximately one third of patients will sustain a new (non-hip) fracture in the next five years (Chapter 3.1), which are known to further increase morbidity and mortality.

Second, physicians may not habitually prescribe AODs to males and to patients eligible for GIOP due to the low body of evidence for the anti-fracture efficacy. The majority of trials have focused on surrogate outcomes (BMD and bone-turnover markers) but were either underpowered to detect or did not assess the influence on fracture risk.[39-41] With regard to these surrogate outcomes, AODs have shown very similar efficacy among males and for GIOP compared to that for post-menopausal osteoporosis. And, recently, two trials have shown

anti-fracture efficacy for (morphometric) vertebral fractures among males with osteoporosis for zoledronate (67% risk reduction),[42] and for denosumab among males receiving androgen-deprivation therapy for prostate cancer.[43] For GIOP, two trials identified a decrease in vertebral fracture risk, one with alendronate[44] and one with risedronate.[45]

Third, reluctance of prescribing or continued use of AODs may result from the occurrence or fear of adverse effects which are frequently reported for the gastrointestinal duct with use of bisphosphonates, although we found no evidence for increased risk of discontinuation with AODs in case of gastro-intestinal complications (Chapter 4.2). It should be noted, however, that in our study it was allowed to switch between AODs which may have occurred in the case of gastro-intestinal complications. The fear for adverse effects may have been strengthened by reports of rare but serious events such as osteonecrosis of the jaw (IR 3-430 per 10 000) and of the ear bone, and atypical fractures of the femur (2-100 per 100 000).[46] Patients and physicians may feel pharmacological fracture prevention does not outweigh these risks but this may be dependent on the absolute fracture risk.

Fourth, in the case of secondary fracture prevention the existence of a communication gap between secondary and primary care is known.[47] And another barrier, which may greatly differ between countries, is the lack of availability of DXA for BMD testing when osteoporotic BMD is used as an intervention threshold.

POTENTIAL MEASURES TO IMPROVE IMPLEMENTATION OF PHARMACOLOGICAL TREATMENT

The development of Fracture Liaison Services (FLS) may provide a great opportunity for bridging the communication gap between the first and the second line for secondary fracture prevention. They have been implemented in a growing number of countries over the last decade where the first FLS was founded in 2003 in the UK. For example in the Netherlands, there are currently 90 FLSs spread amongst almost every hospital where 75% was founded after the year 2007.[48] The core objectives of an FLS are identification of all fracture patients in the particular locality or institution, evidence-based risk assessment (risk stratification, identification of secondary causes of osteoporosis, and fall-risk), initiating of treatment according to relevant guidelines, and improving the long-term adherence with therapy.[47] In the UK, FLSs were founded in 27% of all hospitals until the year 2006, which barely increased to 29% by the year 2009. This may partly explain our finding of a great increase in the prescribing of AODs among British hip fracture patients between the years 2003-2006, and the waning-off of this increase thereafter (Chapter 4.1). Several studies report high persistence with AODs when initiated by an FLS, where 74% to 88% of patients were still on treatment after one year,[49-50] which is similar to the finding in our study (75%) and higher than among first-time users of AODs in general (67%) where the same definition for persistence was used in terms of gap-length and measurement method[51] (Chapter 4.2). This may result from a feeling of greater need of medication due to the experience of a fracture. Furthermore, studies report

FLSs to be cost-effective[47] and report significant reductions in subsequent fracture risk, and even mortality risk, amongst patients treated by an FLS as compared to those not treated by an FLS.[52] However, there is great heterogeneity in quality between FLSs. A recent analysis of 60 FLSs from 20 countries showed especially great heterogeneity in patient identification and risk assessment, where almost one third of all FLSs did not asses fracture risk in more than 50% of non-hip cases, compared to 16% of FLSs for hip cases.[53]

Prior interventions for improving pharmacological prevention of glucocorticoid-induced osteoporosis included education of physicians and/or patients themselves but they were without significant success.[54-58] The community pharmacist may play a central role in the routing of pharmacological prevention since they can identify eligible patients for GIOP in their electronic records. In Chapter 4.4 we have shown, however, that a pharmacy-based intervention resulted in a non-significant increase in the prescribing of bisphosphonates (HR 1.47, 95% CI: 0.91 – 2.39). The set-up of the RCT was very pragmatic where the pharmacists received a list of patients eligible for GIOP (intervention group) and they were asked to provide feedback to the prescribers about importance of GIOP prevention and to prescribe bisphosphonates without any further training of the physicians or patients. Furthermore, randomization was done at the level of the patients and so the intervention effect may have been diluted due to equipoise of the pharmacists where they may have self-identified other eligible patients in the control group but the treatment rates remained very low overall (8% control group, 11.4% intervention group). In post-hoc analyses we did find a significant increase in bisphosphonate prescribing among males and at older age in the intervention group, but this may also be a chance finding since the trial was not originally designed nor sufficiently powered for these subgroup-analyses. We do believe, however, that pharmacy-based approaches require further investigation, where the intervention should be as simple and little time-consuming as possible in order to be implemented in daily practice. Another pharmacy-based approach called "Medication Monitoring and Optimization" (MeMo) has shown to significantly improve persistence with AODs in patients initiating these drugs, which was not specifically for GIOP, where 33% of patients discontinued in the control group over a period of one year, compared to 19% of patients in the intervention group.[59] In this intervention, the pharmacy provided structured counseling on aspects regarding administration, effectiveness, and possible adverse effects with stressing the importance of continuous use. Thereafter, it was actively monitored if patients returned for their repeat prescriptions.

In high-risk individuals who have not sustained a fracture (yet), it may be important to communicate the absolute fracture risk by the use of FRAX. Shared decision making, where the patient and physician can discuss the absolute fracture risk and the accrued benefits and harms from drug treatment, may help to implement drug therapy in those patients likely to benefit most due to their perceived need for treatment. Another advantage of FRAX, is that

treatment may be targeted to high risk patients, where the absolute risk reduction is higher and treatment may become more cost-effective. The validity for use of absolute fracture risk in these respects, however, depends on the accuracy of predicted risk as was outlined before.

CLINICAL RECOMMENDATIONS

The shift from BMD measurement to absolute fracture risk prediction provides an important step forward in the identification of individuals at high fracture risk. However, the clinical utility of fracture risk prediction models for primary prevention in the general community-dwelling population depends on the accuracy of predicted risk, the effectiveness of treatment among those selected, and the acceptance by patients and physicians. With regard to the accuracy of predicted risk, cautiousness in the interpretation of absolute risks is required in the absence of external validation studies that have assessed calibration or when the incorporated fracture/mortality incidence rates are not recent and from a reliable data source. We therefore call for the conduct of such external validation studies for country-specific FRAX models, especially since FRAX becomes implemented in an increasing number of guidelines worldwide without such information. This is true for the general community-dwelling population but also for subgroups where fracture risk prediction is relevant, such as in patients affected by rheumatoid arthritis, after recent fracture, and among nursing-home residents. If predicted risks are accurate, however, the absolute predicted fracture risk can be used for clinical decision making where the absolute risk reduction is greater with higher baseline risk. FRAX without BMD may then be used as an instrument to determine eligibility for BMD assessment, or in case of osteoporotic BMD the absolute risk may be used for shared-decision making for anti-osteoporotic drug treatment. Further research into the effectiveness of anti-osteoporosis drugs among those with high FRAX-based fracture risk but without osteoporosis is needed. In addition, we advocate further research into interactions between absolute fracture risk and efficacy of anti-osteoporosis drug classes.

Importantly, the inadequate uptake of preventive treatment with anti-osteoporosis drugs in high-risk individuals indicates a need for increased awareness about the consequences of fragility fractures and potential benefits of drug treatment (especially for males) among both physicians and patients. For secondary fracture prevention, we advocate the development of Fracture Liaison Services to bridge the care gap. Furthermore, pharmacy-based interventions should be studied further with regard to initiation and continuous use of anti-osteoporosis drugs.

METHODOLOGICAL RECOMMENDATIONS

In the field of absolute fracture risk prediction, many models have been developed but were subsequently not validated in an external population, and if externally validated, calibration was frequently not assessed. The choice of the study design is crucial for validity of external validation studies where the strengths and limitations of the data source(s) used should be known. Electronic retrospective health care records provide large study populations and long-term follow-up but may suffer from under-recording of certain diseases. For example, primary care databases do not completely capture all sustained fractures and linkage to hospitalization records or another source with complete information is required. Furthermore, the underling population of the data source (e.g. community-dwelling only vs. the total population) and the way registries are being linked may influence the incidence of the outcome and the incidence of the outcome may change over time. FRAX has the advantage that it can be temporally calibrated with country-specific fracture/mortality data, but obviously this requires data from a reliable and representative data source. Better fracture registration is required, which especially applies to non-hip fractures. In the Netherlands, an important development is the revived registration of all hospitalizations by a diagnosis code from the year 2016. Because patients with non-hip fractures are frequently not admitted to the hospital, incidence rates of non-hip fractures may be extracted from nationwide claims data if the definition of "incidence" can be made correctly and the quality of the coding system is validated. Alternatively, quality standards indicate the keeping of databases of all identified and evaluated patients in fracture liaison services; if complete and linked this could provide a good source for obtaining nationwide fracture incidence in the Netherlands.

Furthermore, in the case of predictive modeling with competing risks standard survival analysis (Kaplan-Meier life-tables are Cox regression) leads to biased estimates. Instead, the cumulative incidence function and Fine and Gray regression analyses should be used. We also advocate the use of the Net Reclassification Improvement (NRI) over changes in the C-statistic for determining the incremental predictive value of addition or removal of a predictor. Prerequisite for interpretation of NRI results is adequate calibration of the models being compared and the use of a clinical meaningful intervention threshold.

CONCLUSION

The shift from bone mineral density measurement to prediction of absolute fracture risk is an important step forward in the identification of patients at high fracture risk. It provides a tool for shared-decision making for anti-osteoporosis drug treatment, and these drugs can be targeted to those at high baseline risk resulting in a high absolute risk reduction. However, this thesis shows the importance of external validation with assessment of calibration before

widespread use of these models in clinical practice in both the general community-dwelling population but also in subpopulations where fracture risk prediction is relevant such as in rheumatoid arthritis. This is especially important for the FRAX model, which is increasingly being implemented in clinical practice in countries where this information is absent and where non-hip major osteoporotic fracture incidence is frequently imputed. Indeed, our results suggest that this imputation method may result in underestimation of predicted risks for major osteoporotic fractures by FRAX. This points to a need for high quality country-specific fracture incidence data. In addition, our results show that considering exposure to psychotropic drugs and glucocorticoid dose on top of FRAX predictors does not increase predictive performance for hip fracture on the population-level. Essential aspects of the study design for development or evaluation of prediction models in observational data are the nature of the data source, completeness in record keeping, recency of the study period, and use of valid methods for incorporation of competing risks and evaluation of the added predictive value of a predictor.

Finally, this thesis shows insufficient uptake of anti-osteoporosis drugs among those at high fracture risk, despite availability of clinical guidance. This indicates a need for increased awareness of the consequences of fractures. In addition, there is a need for measures to improve this uptake where shared-decision making and pharmacy-based interventions may play an important role.

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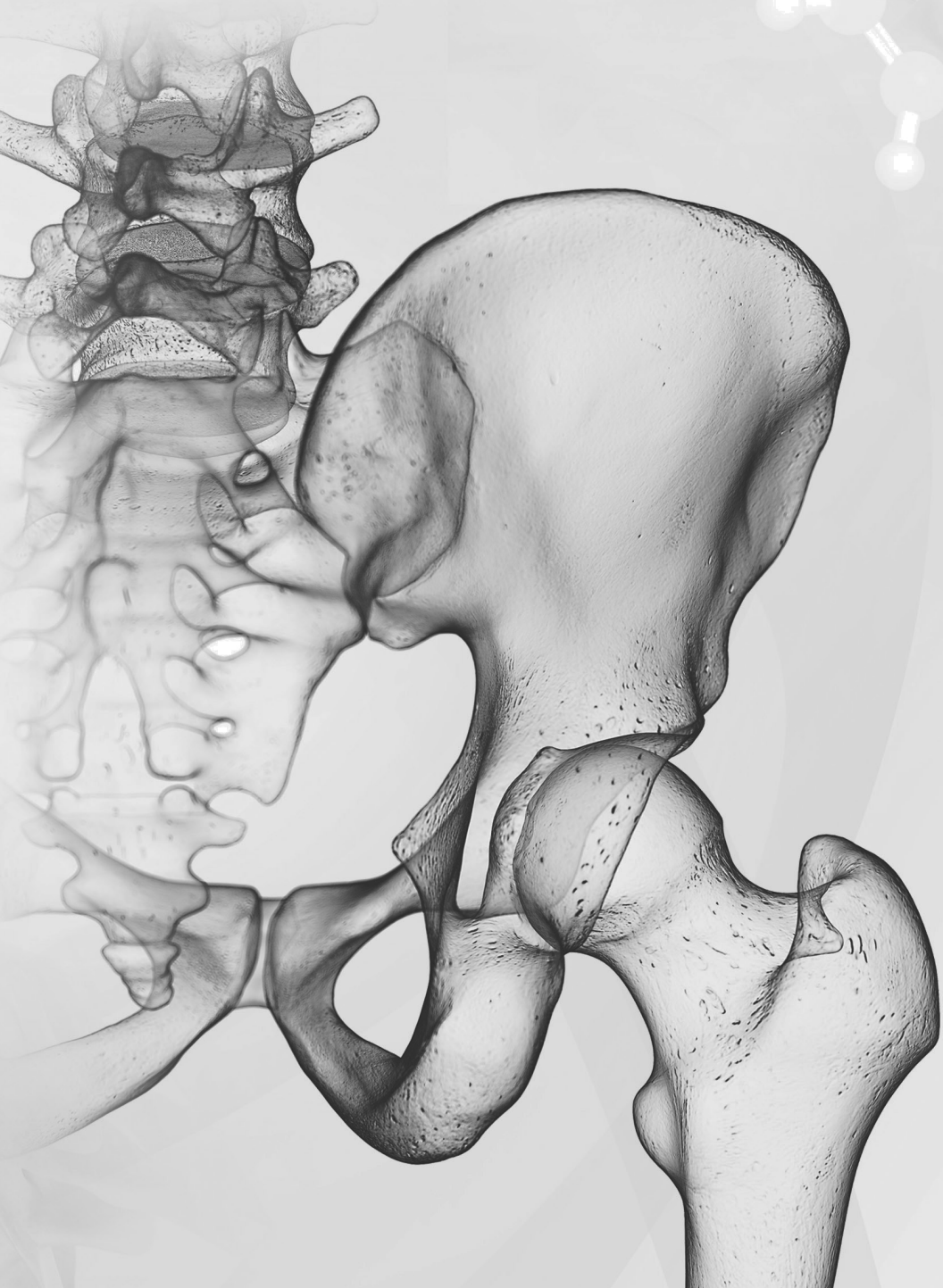
APPENDICES



APPENDIX A1

Summary

SUMMARY

1. INTRODUCTION

Fragility fractures, which typically result from low-energy trauma, are common and are associated with a substantial burden for patients and the healthcare system. They are most frequent at the hip, forearm, spine and humerus and incidence increases with age. Hip fractures in particular are associated with increased morbidity, institutionalisation, and mortality with a mortality rate between 20% and 30% in the first year. This burden is ever increasing due to the ageing of the population. It is therefore important to identify high-risk patients in order to implement preventive measures. One such measure is treatment with anti-osteoporosis drugs which may reduce (subsequent) fracture risk by 30–70%, depending on the drug and fracture site.

Over recent years, the method for identification of individuals at increased fracture risk has shifted from bone mineral density measurement (the amount of minerals in a segment of bone) towards absolute risk assessment where absolute risks are predicted by models that incorporate clinical risk factors (e.g. age, sex, co-morbidities, and drug use) either alone or combined with bone mineral density. The available models, including the most utilized fracture risk prediction tool FRAX, however, have been poorly validated before implementation in clinical guidelines, and several predictors are lacking which may result in reduced predictive performance. Furthermore, a pharmacological care gap has been documented before in high-risk populations. Identification of (patient-related) barriers for implementation would assist in reducing this care gap.

Therefore, the overall thesis aim was to evaluate and to help improve prediction of absolute fracture risk and implementation of pharmacological treatment.

2. ABSOLUTE FRACTURE RISK PREDICTION

First, we studied the validity of the imputation method for incidence of major osteoporotic fracture (MOF; first of hip, forearm, clinical spine, or humerus), which enables prediction of the 10-year risk for this outcome by country-specific FRAX models in the absence of such data **(Chapter 2.1)**. This method assumes equal age-and-sex-specific incidence rate ratios for hip fracture relative to MOF as was observed in Sweden over the period 1987-1996. We found observed MOF incidence to be significantly higher than expected based on the imputation method among women over a wide age-range, where fractures were extracted from both primary care and hospitalisation records in the Dutch PHARMO database network.

In **Chapter 2.2** we studied the predictive performance of the UK version of FRAX in the general population (GP) and in patients with rheumatoid arthritis (RA) using data of the UK Clinical Practice Research Datalink (CPRD) also linked to hospitalisations for hip fracture

(CPRD-HES). We found that UK FRAX significantly overestimated fracture risk in patients with RA, both for MOF (mean predicted vs. observed 10-year risk: 13.3% vs. 8.4%) and for hip fracture (CPRD: 5.5% vs. 3.1%, CPRD-HES: 5.5% vs. 4.1%). In the general population, UK FRAX performed well for hip fracture after linkage to hospitalisations (CPRD-HES: 2.7% vs. 2.4%). Discrimination was good for hip fracture (C-statistic RA and GP: 0.78 and 0.83) and moderate for MOF (0.69 and 0.71). Extension of the recalibrated UK FRAX for hip fracture in CPRD-HES with duration of RA disease, glucocorticoid dose (> 7.5 mg/day), and secondary osteoporosis did not improve predictive performance (Net Reclassification Improvement [NRI]: 0.01, 95% CI: -0.04-0.05, C-statistic 0.78).

Next, we determined whether addition of psychotropic drug classes and glucocorticoid dose to predictors as in FRAX would improve predictive performance for the 10-year risk of hip fracture in the general population **(Chapter 2.3)**. Hip fracture incidence was significantly lower in CPRD than in CPRD-HES, and the latter data source was used for this study. Addition of these predictors did not increase predictive performance. There was a marginal improvement in classification of hip fracture cases (1.24%) with a small deterioration for non-cases (0.24%), yielding an NRI of 0.01 (95% CI: 0.00-0.02). There was no difference in C-statistics (0.87).

3. SUBSEQUENT FRACTURE AND MORTALITY POST-HIP FRACTURE

In **Chapter 3.1** we examined the risk of a subsequent major or any fracture after hip fracture, including its risk factors and a change over calendar time (2000-2010) using data from CPRD. Within 1 year following hip fracture, 2.7% and 8.4% of patients sustained a major or any (non-hip) fracture, which increased to 14.7% and 32.5% after 5 years, respectively. The most important risk factors were female gender and a history of secondary osteoporosis. The annual risk increased during the study period for both subsequent major (2009-2010 vs. 2000-2002: adj. HR 1.44, 95% CI: 1.12-1.83) and any (non-hip) fracture (adj. HR 1.80, 95% CI: 1.58-2.06).

In **Chapter 3.2** we determined whether there was a change in mortality risk post-hip fracture over the period 2000-2010 in CPRD, also linked to death registration data from the Office of National Statistics. One-year all-cause mortality declined from 2009 and was 14% lower after, compared with before 2009 (22.3% to 20.5%, adj. HR 0.86, 95% CI: 0.81-0.92). Significant contributors to this decline were respiratory infections in females and malignant diseases in males. However, the difference in one-year mortality between hip fracture patients and the general population remained unaltered with a 3.5-fold and 2.4-fold increased risk in males and females, respectively.

4. PHARMACOLOGICAL TREATMENT

Using data from CPRD, we examined determinants for anti-osteoporosis drug prescribing after hip fracture in **Chapter 4.1**. Despite a substantial increase in prescribing over the period 2000-2010, prescribing remained inadequate with 54% of hip fracture patients not receiving an anti-osteoporosis drug within one year post-hip fracture in the year 2010. Men, those overweight, having dementia or exposed to antipsychotics, sedatives/hypnotics, and opioid analgesics were significantly less likely to receive anti-osteoporosis drugs following hip fracture.

In **Chapter 4.2** we determined persistence (duration of staying on drug treatment) with anti-osteoporosis drugs and determinants for discontinuation among patients with a recent fracture. This study was conducted within the Dutch PHARMO Database Network. After the first year, 75% was still on treatment which decreased to 45% after 5 years. A significant determinant for early discontinuation was age ≥ 80 years (reference 50-59 years: adj. HR 1.65, 95% CI: 1.15-2.38). We found no significant determinants in the period thereafter. Within 1 year after discontinuation, 24% restarted drug treatment, yet 47% subsequently stayed on treatment for 1 year.

Finally, in **Chapter 4.3** it was determined whether feedback by pharmacists to physicians of patients eligible for glucocorticoid-induced osteoporosis prophylaxis would stimulate the prescribing of anti-osteoporosis drugs (primary outcome was a bisphosphonate) in a randomised clinical trial. Over a mean period of 6.2 months, the intervention did not significantly increase the prescribing of bisphosphonates (11.4% intervention group vs. 8.0% control group; HR 1.47, 95% CI: 0.91-2.39). The prescribing of calcium and vitamin D was also not significantly altered.

5. DISCUSSION

In the general discussion the clinical utility of fracture risk prediction models was discussed along with a discussion about the impact of the study design on development and evaluation of prediction models. We also discussed the barriers and potential measures for improving implementation of pharmacological treatment, and finally the effectiveness of anti-osteoporosis drugs among patients with increased fracture risk according to the FRAX model was discussed.

In our studies, we show the importance of external validation with assessment of calibration before widespread implementation of fracture risk prediction models in clinical practice in both the community-dwelling population but also in subpopulations where fracture risk prediction is relevant such as in patients with rheumatoid arthritis. For predictive modelling, an essential aspect of the study design is completeness of record keeping where we found a significant under recording of hip fractures in general practitioner data as compared to

hospitalisation data. Other aspects of the study design that affect absolute risks are the nature of the data source, the study period, and implementation of competing risks. If predicted risks are accurate, however, the absolute fracture risk can be used for clinical decision making where the absolute risk reduction with anti-osteoporosis drugs is greater with higher baseline risk. Since it is still uncertain whether anti-osteoporosis drugs are efficacious among those with high predicted risk but without information on bone mineral density the absolute risk may be used to determine eligibility for BMD assessment, or in case of osteoporotic BMD the absolute risk may be used for shared-decision making for anti-osteoporotic drug treatment.

In conclusion, fracture risk prediction models, such as the FRAX model, may be valuable tools for identification of high-risk patients and for risk communication, but we stress the importance of external validation with assessment of calibration before use in clinical practice. This requires a complete and valid registration of fractures which needs to be improved for non-hip fractures in the Netherlands. Furthermore, the inadequate uptake of preventive treatment with anti-osteoporosis drugs indicates a need for increased awareness about the consequences of fragility fractures, with high post-hip fracture mortality and subsequent fracture rates, among both physicians and patients and a need for additional measures to improve this.

APPENDIX A2

Samenvatting

SAMENVATTING

1. INTRODUCTIE

Botbreuken, ontstaan door laag energetisch trauma, komen vaak voor en zijn geassocieerd met een aanzienlijke last voor patiënten en het zorgstelsel. Ze komen het meest frequent voor in de heup, voorarm, wervelkolom, en de humerus en de incidentie stijgt met toenemende leeftijd. Met name heupbreuken zijn geassocieerd met een verhoogde morbiditeit, institutionalisering, en sterfte met een sterfte percentage tussen de 20% en 30% in het eerste jaar. Deze last zal blijven toenemen door de vergrijzing van de bevolking. Het is daarom belangrijk om hoog-risico patiënten te kunnen identificeren om preventieve maatregelen te kunnen nemen. Eén van de maatregelen is behandeling met anti-osteoporose medicatie, waarmee het risico op een (volgende) botbreuk met 30-70% gereduceerd kan worden, afhankelijk van het type medicatie en de locatie van de botbreuk.

Sinds enkele jaren is de methode om hoog-risico patiënten te identificeren verschoven van het meten van de botmineraaldichtheid (de hoeveelheid aan mineralen in een botsegment) naar evaluatie van het absolute risico, waar absolute risico's worden voorspeld door modellen die klinische risicofactoren (zoals leeftijd, geslacht, co-morbiditeit, en medicatie gebruik) combineren, soms ook tezamen met botmineraaldichtheid. De beschikbare modellen, inclusief het meest toegepaste model om botbreuken te voorspellen, FRAX, zijn echter onvoldoende gevalideerd alvorens geïmplementeerd in klinische richtlijnen. Ook ontbreken er verschillende risicofactoren wat kan resulteren in een verminderde voorspellende prestatie. Voorheen is gedocumenteerd dat farmacologische behandeling van hoog-risico populaties tekort schiet. Identificatie van (patiënt-gerelateerde) belemmeringen voor de uitvoering hiervan zou kunnen helpen om dit te verbeteren.

Het doel van dit proefschrift was daarom om het voorspellen van het absolute risico op botbreuken en de implementatie van farmacologische behandeling te evalueren en te helpen verbeteren.

2. VOORSPELLEN VAN HET ABSOLUTE RISICO OP BOTBREUKEN

In de eerste studie is de validiteit van de imputatie methode voor incidentie van de belangrijkste osteoporotische botbreuken (MOF; eerste breuk van de heup, voorarm, wervel indien symptomatisch, of humerus) onderzocht. Met deze methode wordt de voorspelling van het 10-jaars risico op deze uitkomst door land-specifieke FRAX modellen mogelijk gemaakt indien deze data ontbreekt **(hoofdstuk 2.1)**. Deze methode gaat ervan uit dat de incidentie rate ratio's voor heupbreuken ten opzichte van MOF breuken, voor specifieke leeftijdscategorieën en geslacht, gelijk zijn aan de ratio's die werden geobserveerd in Zweden over de periode 1987-1996. De geobserveerde MOF incidentie was significant hoger dan verwacht volgens de imputatie methode bij vrouwen over een brede leeftijdsrange. Botbreuken werden in

deze studie geëxtraheerd door middel van huisartsen diagnosecodes en hospitalisatie codes afkomstig uit het Nederlandse PHARMO database netwerk.

In **hoofdstuk 2.2** is de voorspellende waarde van het FRAX model (Verenigd Koninkrijk versie; UK) onderzocht in de algemene bevolking (GP) en in patiënten met reumatoïde artritis (RA) met behulp van diagnosecodes uit de UK Clinical Practice Research Datalink (CPRD) en er werd ook gekoppeld aan hospitalisatie codes voor heupbreuken (CPRD-HES). Het Britse FRAX model overschatte het 10-years risico op botbreuken significant in patiënten met RA, zowel voor MOF breuken (gemiddeld voorspelt vs. geobserveerd 10-years risico: 13,3% vs. 8,4%) als voor heup breuken (CPRD: 5,5% vs. 3,1%, CPRD-HES: 5,5% vs. 4,1%). In de algemene bevolking presteerde het Britse FRAX model goed voor heupbreuken na koppeling aan hospitalisaties (CPRD-HES: 2,7% vs. 2,4%). Discriminatie was goed voor heupbreuken (C-statistic RA en GP: 0,78 en 0,83) en voldoende voor MOF (0,69 en 0,71). Extensie na re-kalibratie van het Britse FRAX model voor heupbreuken met ziekteduur van RA, glucocorticoïd dosering (> 7.5 mg/dag), en secundaire osteoporose verbeterde de voorspellende waarde niet bij patiënten met RA (Net Reclassification Improvement [NRI]: 0,01, 95% BI: -0,04-0,05, C-statistic 0,78).

Vervolgens is onderzocht of toevoeging van psychotrope medicatie en de dosering glucocorticoïden aan predictoren zoals in het FRAX model de voorspellende waarde voor het 10-jaars risico op heupbreuken kon verbeteren in de algemene populatie **(hoofdstuk 2.3)**. De incidentie voor heup breuken was significant lager in CPRD dan in CPRD-HES, en de laatste databron werd daarom gebruikt voor deze studie. Toevoeging van deze predictoren verbeterde de voorspellende waarde niet. Er was een marginale verbetering in de classificatie van patiënten met heupbreuken (1,24%), en een kleine verslechtering in de classificatie van patiënten zonder heup breuken (0,24%), wat leidde tot een NRI van 0,01 (95% BI: 0,00-0,02). Er was geen verschil in C-statistic tussen de modellen (0,87).

3. NIEUWE BOTBREUKEN EN STERFTE NA EEN HEUPBREUK

In **hoofdstuk 3.1** is het risico op een nieuwe MOF breuk of een breuk ongeacht de locatie (m.u.v. heupbreuken) na een heupbreuk onderzocht. Hierbij zijn ook risicofactoren en een verandering over de kalendertijd (2000-2010) onderzocht met behulp van data uit CPRD. Binnen 1 jaar na een heupbreuk, onderging respectievelijk 2,7% en 8,4% van de patiënten een nieuwe MOF breuk of een breuk ongeacht de locatie. Dit nam respectievelijk toe tot 14,7% en 32,5% over een periode van 5 jaar. De belangrijkste risicofactoren waren het vrouwelijk geslacht en een geschiedenis van secundaire osteoporose. Het jaarlijkse risico nam toe gedurende de studie periode zowel voor een nieuwe MOF breuk (2009-2010 vs. 2000-2002: adj. HR 1,44, 95% BI: 1,12-1,83) als voor een nieuwe (niet-heup) breuk ongeacht de locatie (adj. HR 1,80, 95% BI: 1,58-2,06).

In **hoofdstuk 3.2** werd het risico op sterfte na een heupbreuk bestudeerd over de periode 2000-2010. Data werd geëxtraheerd uit CPRD en werd ook gekoppeld aan mortaliteitsgegevens afkomstig van het Britse Bureau voor de Statistiek. Het 1-jaars risico op sterfte door alle oorzaken nam af vanaf het jaar 2009 en was 14% lager na, in vergelijking met voor het jaar 2009 (22,3% naar 20,5%, adj. HR 0,86, 95% BI: 0,81-0,92). Dit werd mede gedreven door een significante daling in het risico op sterfte door infecties van de luchtwegen bij vrouwen en in het risico op sterfte door maligne aandoeningen bij mannen. Het verschil in 1-jaars sterfte tussen patiënten met een heupbreuk en de algemene bevolking bleef echter ongewijzigd met een respectievelijk 3,5-voudig en 2,4-voudig verhoogd sterfterisico voor mannelijke en vrouwelijke heupbreuk patiënten.

4. FARMACOLOGISCHE BEHANDELING

Met behulp van data uit CPRD werden determinanten voor het voorschrijven van anti-osteoporose medicatie na een heupbreuk onderzocht in **hoofdstuk 4.1**. Ondanks een substantiële toename in het voorschrijven over de periode 2000-2010, bleef dit ontoereikend waarbij 54% van de patiënten met een heupbreuk geen anti-osteoporose medicatie ontving in het eerste jaar na de breuk in het jaar 2010. Mannen, patiënten met overgewicht, en patiënten met dementie of die waren blootgesteld aan antipsychotica, sedativa/hypnotica, of opioïden hadden significant minder kans om anti-osteoporose medicatie te krijgen na hun heupbreuk.

In **hoofdstuk 4.2** werd de gebruiksduur van anti-osteoporose medicatie (persistentie; de tijd dat een geneesmiddel achtereen gebruikt wordt) geëvalueerd en werden determinanten voor stoppen onderzocht bij patiënten die recent een bot hadden gebroken. Deze studie is uitgevoerd in het Nederlandse PHARMO Database Netwerk. Over een periode van 1 jaar na starten bleef 75% van de patiënten hun anti-osteoporose medicatie gebruiken, wat daalde naar 45% na een periode van 5 jaar. Een significante determinant voor het vroegtijdig stoppen (binnen 1 jaar) met de anti-osteoporose medicatie was een leeftijd van ≥ 80 jaar (referentie 50-59 jaar: adj. HR 1,65, 95% BI: 1,15-2,38). Er werden geen determinanten gevonden voor stoppen in de periode hierna. Binnen 1 jaar na stoppen, bleek 24% opnieuw te starten met anti-osteoporose medicatie, maar 47% van deze patiënten bleef deze medicatie doorgebruiken gedurende minstens 1 jaar.

Tenslotte is in **hoofdstuk 4.3** onderzocht of feedback door apothekers aan artsen over het belang van medicamenteuze profylaxe van door glucocorticoïd geïnduceerde osteoporose het voorschrijven van anti-osteoporose medicatie zou bevorderen in deze patiënten groep in een gerandomiseerde klinische studie (de primaire uitkomstmaat was een verstrekking van een bisfosfonaat). Over een periode van gemiddeld 6,2 maanden bleek de interventie geen significante invloed te hebben op het voorschrijven van bisfosfonaten (11,4% interventiegroep versus 8,0 % controlegroep ; HR 1,47, 95% BI: 0,91-2,39). Ook was er geen significant effect op het voorschrijven van calcium en vitamine D.

5. DISCUSSIE

In de discussie van dit proefschrift is de klinische utiliteit van de modellen die het absolute risico op botbreuken voorspellen besproken, tezamen met de invloed van de studieopzet op de ontwikkeling en evaluatie van deze modellen. Daarnaast werden de barrières voor implementatie van farmacologische behandeling en de potentiele maatregelen om dit te verbeteren besproken. Tenslotte werd ingegaan op de effectiviteit van anti-osteoporose medicatie bij patiënten met een verhoogd risico op botbreuken zoals voorspeld door het FRAX model.

Dit proefschrift laat zien dat het belangrijk is om modellen die het risico op botbreuken voorspellen extern te valideren, waarbij ook de kalibratie moet worden geëvalueerd, alvorens gebruik in de klinische praktijk. Dit geldt voor zowel de algemene populatie alsook voor populaties waarbinnen het voorspellen van het botbreuk risico relevant is, zoals bij patiënten met reumatoïde artritis. Indien predictie modellen worden ontwikkeld of geëvalueerd moet er sprake zijn van een volledige en valide registratie van diagnose codes. In dit proefschrift werd gevonden dat heupbreuken niet volledig worden geregistreerd in de systemen van huisartsen wanneer werd vergeleken met ziekenhuisopnames. Andere aspecten van de studieopzet die het voorspelde absolute risico kunnen beïnvloeden, zijn de aard van de databron, de studieperiode, en de implementatie van concurrerende risico's. Indien de voorspelde risico's echter accuraat zijn, kan het absolute risico worden gebruikt voor klinische besluitvorming waar de absolute risicoreductie die kan worden bereikt met anti-osteoporose medicatie groter is indien het uitgangsrisico hoger is. Het is echter nog onzeker of anti-osteoporose medicatie werkzaam is bij mensen met een verhoogd absoluut risico, op basis van bijvoorbeeld het FRAX model, zonder gegevens over de botmineraaldichtheid waardoor onzeker is of er ook sprake is van osteoporose. Totdat hierover meer duidelijkheid komt, kan het voorspelde absolute risico worden gebruikt om kandidaten voor een BMD meting te selecteren, en, indien er wel sprake is van een osteoporotische BMD, kan het absolute risico worden gebruikt voor de gezamenlijke besluitvorming voor het starten van behandeling met anti-osteoporotische geneesmiddelen.

Als conclusie kan worden gesteld dat modellen die het absolute botbreuk risico voorspellen, zoals het FRAX model, waardevol kunnen zijn voor het identificeren van hoog-risico patiënten en voor risico communicatie, maar dat deze modellen extern gevalideerd moeten worden waarbij ook de kalibratie wordt onderzocht voordat ze worden geïmplementeerd in de klinische praktijk. Dit vereist een volledige en valide registratie van botbreuken, wat moet worden verbeterd voor niet-heupbreuken in Nederland. Bovendien wijst de gebrekkige opname van behandeling met anti-osteoporose medicatie op het belang van meer bewustwording over de gevolgen van botbreuken onder zowel artsen als patiënten, met een hoog risico op sterfte na een heupbreuk en een hoog risico op nieuwe botbreuken, en zijn er aanvullende maatregelen nodig om deze implementatie te verbeteren.

APPENDIX A3

Dankwoord

DANKWOORD

Als kind zei ik al dat ik later "onderzoek wilde gaan doen" en dan nu, jaren later, heb ik mijn promotieonderzoek afgerond. Ik ben dankbaar dat ik deze kans heb gekregen en ik ben mijn dank verschuldigd aan velen die hebben geholpen om deze mijlpaal te bereiken.

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APPENDIX A5

List of publications

LIST OF PUBLICATIONS

PUBLICATIONS RELATED TO THIS THESIS

Klop C, de Vries F, Bijlsma JWJ, Leufkens HGM, Welsing PMJ. Predicting the 10-year risk of hip and major osteoporotic fracture in rheumatoid arthritis and in the general population: an independent validation and update of UK FRAX without bone mineral density. Ann Rheum Dis 2016; published online first. doi: 10.1136/annrheumdis-2015-208958.

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