RESEARCH ARTICLE

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Estimating the Incidence and Key Risk Factors of Cardiovascular Disease in Patients at High Risk of Imminent Fracture Using Routinely Collected Real-World Data From the UK

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ABSTRACT

The objective of this work was to estimate the incidence rate of cardiovascular disease (CVD) events (myocardial infarction, stroke, or CVD death) at 1 year among three cohorts of patients at high risk of fracture (osteoporosis, previous fracture, and anti-osteoporosis medication) and to identify the key risk factors of CVD events in these three cohorts. To do so, this prospective cohort study used data from the Clinical Practice Research Datalink, a primary care database from United Kingdom. Major adverse cardiovascular events (MACE, a composite outcome for the occurrence of either myocardial infarction [MI], stroke, or CVD death) were identified in patients aged 50 years or older at high or imminent fracture risk identified in three different cohorts (not mutually exclusive): recently diagnosed with osteoporosis (OST, $n = 65,295$), incident fragility fracture (IFX, $n = 67,065$), and starting oral bisphosphonates (OBP, $n = 145,959$). About 1.90%, 4.39%, and 2.38% of the participants in OST, IFX, and OBP cohorts, respectively, experienced MACE events. IFX was the cohort with the higher risk: MACE incidence rates (cases/1000 person-years) were 19.63 (18.54–20.73) in OST, 52.64 (50.7–54.5) in IFX, and 26.26 (25.41–27.12) in OBP cohorts. Risk of MACE events at 1 year was predicted in the three cohorts. Models using a set of general, CVD, and fracture candidates selected by lasso regression had a good discrimination (≥70%) and internal validity and generally outperformed the models using only the CVD risk factors of general population listed in QRISK tool. Main risk factors common in all MACE models were sex, age, smoking, alcohol, atrial fibrillation, antihypertensive medication, prior MI/stroke, established CVD, glomerular filtration rate, systolic blood pressure, cholesterol levels, and number of concomitant medicines. Identified key risk factors highlight the differences of patients at high risk of fracture versus general population. Proposed models could improve prediction of CVD events in patients with osteoporosis in primary care settings. © 2022 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: OSTEOPOROSIS; ORAL BISPHONATES; CARDIOVASCULAR RISK ASSESSMENT; INCIDENCE RATES; PROGNOSTIC MODEL

Introduction

Cardiovascular disease (CVD) and osteoporosis are both leading causes of morbidity and mortality[1,2] worldwide and their prevalence increases with age.[3,4] Several prediction tools have been developed for cardiovascular events (heart attacks or stroke), including the Framingham Heart Study,[5-7] CHADS2 tool,[8-10] and QRISK tool.[11,12] These tools have been developed in general, usually younger, populations and have not been validated in patients with osteoporosis.

Identification of CVD risk factors is particularly challenging for patients with osteoporosis because the association between fracture risk or anti-osteoporosis treatment and cardiovascular events remains unclear.[13] Some established risk factors for osteoporosis and fractures,[14] such as female sex and low weight, have been found to be protective against CVD. Conversely, some other risk factors, including age, low bone mineral density,[15] prior fracture, obesity,[16-18] or type 2 diabetes,[19] are associated with an increased risk of CVD. Patients with a history of CVD have been shown to be at increased risk of osteoporotic fractures,[20] whereas higher risk of stroke and coronary artery disease is observed among patients with osteoporotic fracture or low bone mineral density.[21]

The effects of anti-osteoporosis medications on CVD risk is inconclusive: despite no evidence from clinical trials that oral bisphosphonates (BP) have an impact on cardiovascular risk,[22,23] some publications suggest a protective effect.[24] Meanwhile, the European Medicines Agency (EMA) has advised contraindications to patients with a history of prior myocardial infarction (MI) or stroke regarding romosozumab, the most recent medication option for osteoporosis,[25] in addition to the preexisting restrictions to menopausal hormone therapy[26] and strontium ranelate.[27] This variable impact of anti-osteoporotic medication on CVD risk highlights the clinical utility of identifying patients who are being considered for osteoporosis treatment and might be at elevated risk of CVD.

To address this issue, our overarching aim was to assess the absolute risk of CVD experienced by elderly patients at higher fracture risk in the UK, as well as to identify key CVD risk factors (both generic and specific ones) for these patients. We estimate incidence rates of major adverse cardiovascular events (MACE) among cohorts newly diagnosed with osteoporosis, those with first recorded fracture, and oral BP therapy initiators obtained from the UK general population, and developed and internally validated models that predict 1-year MACE in these cohorts of high-risk patients. Additionally, a secondary analysis of 2-year MACE and a sensitivity analysis for MI/stroke prediction is reported.

Subjects and Methods

Data source

Data for this study were obtained from the Clinical Practice Research Datalink (CPRD) GOLD, which contains anonymized electronic primary care records for the UK (www.cprd.com/primarycare). In addition to demographic information, the data included medication prescriptions, clinical events, tests, referrals, and hospital admissions along with their major outcomes in a sample of >16 million patients (including deceased and transferred out; 2.3 million are current patients, covering approximately 3.6% of UK population).[28,29] For this study, an extract from January 1, 1995, to January 31, 2017, was used. We used CPRD GOLD data linked to the Hospital Episode Statistics (HES) Admitted Patient Care, which contains clinical diagnoses during hospital admissions in England, to the Office for National Statistics (ONS) mortality records, and to the Index of Multiple Deprivation (IMD) data set. We reconciled CPRD GOLD and ONS mortality dates of death following published guidelines.[30]

Participants

The study population included patients at high or imminent fracture risk as identified from literature, divided into three cohorts:

1. Patients with an incident diagnosis of osteoporosis (read or ICD-10 codes). We refer to this group as the osteoporosis cohort (OST).
2. Patients with a first incident fracture at an osteoporotic site (all except face, skull, and digits), diagnosed either through read codes or ICD-10 codes. This cohort is referred to as the imminent fracture risk cohort (IFX).
3. Incident users of oral bisphosphonates (BP) without BP use in the prior year, referred to as the oral BP treatment cohort (OBP).

Index date was defined as time of recorded incident diagnosis, first incident fracture, and incident use of BP, for the OST, IFX, and OBP cohorts, respectively. Participants were followed from index date up to a maximum of 2 years. We censored participants at the earliest of first: study outcome, death, transfer out of practice, or the end of follow-up period. Included patients were at least 50 years old and had at least 1 year of data available before index date. Participants could potentially be present in more than one of the cohorts above, with different index dates. For OBP cohort, subjects with use of any anti-osteoporotic drug (except calcium and vitamin D supplements) in the previous year were excluded.

In the IFX cohort, high risk of imminent fracture was defined following Kanis and colleagues[31] designation: imminent risk period is the following 2-year period after a fracture.[32]

Candidate risk factors

The overall set of variables considered for inclusion in the prediction model contained risk factors from the QRISK model,[12] as well as additional risk factors identified in the literature as being potentially associated with CVD.[15-17,20,21,33-41] These included sociodemographic and lifestyle factors, laboratory measurements, medications, and comorbidities (Table 1).

Outcomes

The main outcome of the study was 1-year occurrence of MACE, a composite outcome of the first occurrence of either stroke, MI, or death due to CVD (recorded as the primary cause of death in ONS).

Additionally, secondary analysis of 2-year occurrence of MACE and sensitivity analysis excluding death (MI/stroke) at 1 and 2 years is reported in the Supplemental Data: MI/stroke, a composite outcome of the first occurrence of either stroke or MI.

Statistical analysis

Baseline characteristics of all three cohorts were described.

Estimation of incidence rates

Incidence rates (IR) and their 95% confidence interval of each outcome at 1 and 2 years after index date were calculated (cases/1000 person-years) through ERIC Notebook person-time methodology.[42]

Construction of the prediction models

Performance of QRISK variables to estimate the 1-year risk of MACE was assessed (QRISK variables are listed in Supplemental Table S1). Finally, all the available candidate risk factors described in the above were combined into a prediction model (henceforth referred to as "ALL"). Lasso

Table 1. Baseline Characteristics of Patients in the Development Set and the Validation Set

Variable	OST n = 65,295	IFX n = 67,065	OBP n = 145,959
Sex, male (%)	8616 (13.2)	16,386 (24.4)	29,547 (20.2)
Age >75 years	31,105 (47.6)	48,726 (72.7)	77,199 (52.9)
Age group, years (%)			
50–59	8315 (12.7)	4764 (7.1)	16,388 (11.2)
60–69	15,949 (24.4)	7646 (11.4)	31,665 (21.7)
70–79	21,165 (32.4)	15,573 (23.2)	45,679 (31.3)
80–89	16,586 (25.4)	27,546 (41.1)	42,053 (28.8)
>89	3280 (5.0)	11,536 (17.2)	10,174 (7.0)
SES (%)			
1	15,953 (24.4)	14,980 (22.3)	35,837 (24.6)
2	15,643 (24.0)	15,990 (23.8)	35,738 (24.5)
3	13,794 (21.1)	14,322 (21.4)	30,877 (21.2)
4	11,921 (18.3)	12,892 (19.2)	26,566 (18.2)
5	7918 (12.1)	8820 (13.2)	16,828 (11.5)
Smoking[a] (%)			
Ex	20,487 (31.4)	21,484 (32.0)	50,162 (34.4)
No	34,049 (52.1)	35,272 (52.6)	75,838 (52.0)
Yes	10,759 (16.5)	10,309 (15.4)	19,959 (13.7)
Drinking[a] (%)			
Ex	3564 (5.5)	3945 (5.9)	7226 (5.0)
No	17,062 (26.1)	21,092 (31.5)	41,791 (28.6)
Yes	44,669 (68.4)	42,028 (62.7)	96,942 (66.4)
Diabetes type I[b] (%)	152 (0.2)	164 (0.2)	297 (0.2)
Diabetes type II[b] (%)	3311 (5.1)	4171 (6.2)	8340 (5.7)
Chronic obstructive pulmonary disease[b] (%)	4939 (7.6)	3745 (5.6)	11251 (7.7)
Chronic kidney disease[b] (%)	5790 (8.9)	8117 (12.1)	13396 (9.2)
Rheumatoid arthritis[b] (%)	5045 (7.7)	2891 (4.3)	19746 (13.5)
Lupus[b] (%)	144 (0.2)	55 (0.1)	328 (0.2)
Systemic heart disease[a] (%)	2341 (3.6)	563 (0.8)	5222 (3.6)
Anti-osteoporosis use[a] (%)	11752 (18.0)	5356 (8.0)	
Heparin use[a] (%)	372 (0.6)	282 (0.4)	1035 (0.7)
Beta-blocker use[a] (%)	10564 (16.2)	10392 (15.5)	22753 (15.6)
Hypertension[a] (%)	5091 (7.8)	3334 (5.0)	9514 (6.5)
Deep vein thrombosis or pulmonary embolism[a] (%)	522 (0.8)	439 (0.7)	1334 (0.9)
Anticoagulant use[a] (%)	3285 (5.0)	3536 (5.3)	7546 (5.2)
Antidepressants TCA[a] (%)	7039 (10.8)	5352 (8.0)	14,451 (9.9)
Antidepressants SSRI[a] (%)	5990 (9.2)	7293 (10.9)	12651 (8.7)
Hypercholesterolemia[a] (%)	1561 (2.4)	667 (1.0)	2543 (1.7)
Statin use[a] (%)	15571 (23.8)	14084 (21.0)	33,988 (23.3)
Osteoporosis history[b]	NA	5521 (8.2)	46215 (31.7)
Family history of cardiovascular disease (%)	6755 (10.3)	4036 (6.0)	13204 (9.0)
Family history of cardiovascular disease before age 60 years (%)	99 (0.2)	47 (0.1)	170 (0.1)
Heart failure[b] (%)	2323 (3.6)	3405 (5.1)	5040 (3.5)
Migraine[b] (%)	10103 (15.5)	6294 (9.4)	19961 (13.7)
Severe mental illness[b] (%)	10203 (15.6)	8836 (13.2)	19256 (13.2)
Vascular disease[b] (%)	839 (1.3)	1078 (1.6)	1765 (1.2)
Atrial fibrillation[b] (%)	3664 (5.6)	4784 (7.1)	8022 (5.5)
On antihypertensive drug (%)	37053 (56.7)	38036 (56.7)	79044 (54.2)
Antipsychotic use[a] (%)	371 (0.6)	867 (1.3)	773 (0.5)
Steroid use[a] (%)	9367 (14.3)	5181 (7.7)	37201 (25.5)
Erectile dysfunction[a] (%)	871 (1.3)	1065 (1.6)	2797 (1.9)
Charlson score (%)			
0	37,782 (57.9)	40,024 (59.7)	80,717 (55.3)
1	13,274 (20.3)	11,209 (16.7)	31,132 (21.3)
2	7960 (12.2)	7388 (11.0)	18,141 (12.4)
≥3	6279 (9.6)	8444 (12.6)	15,969 (10.9)

(Continues)

Table 1. Continued

Variable	OST $n = 65,295$	IFX $n = 67,065$	OBP $n = 145,959$
Cardiovascular disease (%)			
No	58,034 (88.9)	58,381 (87.1)	128,516 (88.0)
Ever >1 year before index date	5616 (8.6)	6996 (10.4)	13,474 (9.2)
1 year before index	719 (1.1)	743 (1.1)	1551 (1.1)
6 months before index	723 (1.1)	767 (1.1)	1763 (1.2)
1 month before index	203 (0.3)	178 (0.3)	655 (0.4)
MI or stroke (%)			
No	61,350 (94.0)	60,046 (89.5)	135,335 (92.7)
Ever >1 year before index date	2850 (4.4)	5083 (7.6)	7481 (5.1)
1 year before index	1095 (1.7)	1936 (2.9)	3143 (2.2)
Established CVD[b] = ever (%)	7428 (11.4)	11,506 (17.2)	18,774 (12.9)
Any fracture history (%)			
No	49,542 (75.9)	67,065 (100)	114,386 (78.4)
Ever >1 year before index date	5813 (8.9)	0	10,598 (7.3)
1 year before index	9940 (15.2)	0	20,975 (14.4)
Hip fracture history (%)			
No	62,040 (95.0)	67,065 (100)	136,610 (93.6)
Ever >1 year before index date	1118 (1.7)	0	1720 (1.2)
1 year before index	2137 (3.3)	0	7629 (5.2)
Shoulder fracture history (%)			
No	64,836 (99.3)	67,065 (100)	145,199 (99.5)
Ever >1 year before index date	232 (0.4)	0	333 (0.2)
1 year before index	227 (0.3)	0	427 (0.3)
Spine fracture history (%)			
No	63,880 (97.8)	67,065 (100)	143,554 (98.4)
Ever >1 year before index date	326 (0.5)	0	356 (0.2)
1 year before index	1089 (1.7)	0	2049 (1.4)
Wrist fracture history (%)			
No	60,237 (92.3)	67,065 (100)	137,118 (93.9)
Ever >1 year before index date	2363 (3.6)	0	4040 (2.8)
1 year before index	2695 (4.1)	0	4801 (3.3)
BMI[a] (%)			
<18.5	5615 (8.6)	9265 (13.8)	10,877 (7.5)
18.6–24.9	32,564 (49.9)	33,554 (50.0)	66,542 (45.6)
25–29.9	18,343 (28.1)	16,720 (24.9)	44,109 (30.2)
30–39.9	8164 (12.5)	6983 (10.4)	22,452 (15.4)
≥40	609 (0.9)	543 (0.8)	1979 (1.4)
No. of GP visits[a] (%)			
0	3219 (4.9)	15,017 (22.4)	15,177 (10.4)
1–5	16,176 (24.8)	15,528 (23.2)	36,213 (24.8)
6–10	17,452 (26.7)	13,677 (20.4)	32,344 (22.2)
11–15	11,938 (18.3)	9140 (13.6)	24,466 (16.8)
≥16	16,510 (25.3)	13,703 (20.4)	37,759 (25.9)
No. of GP emergency visits[a] (%)			
0	53,095 (81.3)	53,221 (79.4)	119,698 (82.0)
1	6570 (10.1)	6392 (9.5)	14,083 (9.6)
2	2439 (3.7)	2844 (4.2)	5282 (3.6)
3–5	2282 (3.5)	3163 (4.7)	4993 (3.4)
≥6	909 (1.4)	1445 (2.2)	1903 (1.3)
eGFR[a] (%)			
≤29	708 (1.1)	1974 (2.9)	1777 (1.2)
30–44	3470 (5.3)	7099 (10.6)	9749 (6.7)
45–59	11,950 (18.3)	15,335 (22.9)	30,290 (20.8)
60–89	45,497 (69.7)	39,774 (59.3)	96,838 (66.3)
≥90	3670 (5.6)	2883 (4.3)	7305 (5.0)
SBP[a] (%)			
<120	9076 (13.9)	9184 (13.7)	18,549 (12.7)

(Continues)

Table 1. Continued

Variable	OST n = 65,295	IFX n = 67,065	OBP n = 145,959
120–139	26,605 (40.7)	25,872 (38.6)	57,685 (39.5)
140–159	22,588 (34.6)	23,213 (34.6)	51,589 (35.3)
≥160	7026 (10.8)	8796 (13.1)	18,136 (12.4)
DBP[a] (%)			
<80	33,729 (51.7)	36,247 (54.0)	75,132 (51.5)
80–89	24,505 (37.5)	23,468 (35.0)	53,798 (36.9)
90–99	5764 (8.8)	5732 (8.5)	13,678 (9.4)
≥100	1297 (2.0)	1618 (2.4)	3351 (2.3)
No. of concomitant medicines[a] (%)			
0	5171 (7.9)	16,072 (24.0)	20,662 (14.2)
1–3	12,858 (19.7)	10,222 (15.2)	26,686 (18.3)
4–6	14,446 (22.1)	12,572 (18.7)	29,125 (20.0)
7–9	12,375 (19.0)	10,930 (16.3)	26,049 (17.8)
10–12	8788 (13.5)	7675 (11.4)	18,868 (12.9)
≥13	11,657 (17.9)	9594 (14.3)	24,569 (16.8)
Cholesterol measurement[a] (HDL/LDL) (%)			
≤3.5	39,143 (59.9)	42,892 (64.0)	86,247 (59.1)
3.6–5	20,792 (31.8)	18,630 (27.8)	46,654 (32.0)
>5	5360 (8.2)	5543 (8.3)	13,058 (8.9)
No. of previous fractures[b] (%)			
0	46,551 (71.3)	NA	112,120 (76.8)
1	9763 (15.0)	NA	18,129 (12.4)
≥2	8981 (13.8)	NA	15,710 (10.8)

OST = patients with incident diagnosis of osteoporosis; IFX = patients with incident fragility fracture; OBP = incident users of oral bisphosphonates; SES = socioeconomic status; MI = myocardial infarction; BMI = body mass index; eGFR = estimated glomerular filtration rate; SBP = cholesterol, systolic blood pressure; DBP = diastolic blood pressure.

[a]In the year before start.
[b]Ever.

regression selected the key risk factors, which were then entered into a final logistic regression equation. Model performance was evaluated for this final equation and model coefficients and intercept terms reported. Missing data were handled using multiple imputation and combined using Rubin's rules as required.[43] The data were split 50-50 into training and validation datasets. All models were developed using training data and tested using the validation data. Supplemental Fig. S1 describes the steps used to build the final model. Further explanations of the prediction model development are described in Supplemental Materials.

The same steps were repeated for 2-year MACE (secondary analysis), for 1- and 2-year MI/stroke outcomes (sensitivity analysis) and for sex-based models, included in Supplemental Materials.

Model performance

We assessed the models internally using the validation data sets. Discrimination was evaluated by calculating the area under the curve (AUC). The AUC was produced for all 20 validation data sets, then pooled using Rubin's rules. Calibration was assessed by producing calibration plots of observed versus predicted probabilities, in tenths of predicted risk. Calibration plots were also produced for 10-year age groups and sex.

All statistical analyses took place in R version 3.6.0, including MICE, glmnet, rpart, gbm, caret, flextable, pROC, and officer packages.

Patient and public involvement

Used data were previously collected and all participant records were linked-anonymized. Hence, no patients or members of the public were directly implicated in the design or analysis of the reported data.

Results

A total of 65,295, 67,065, and 145,959 participants were included in the OST, IFX, and OBP cohorts, respectively (Fig 1). Most of the cohorts were populated by women (OST: 86.80%; IFX: 76.7%; OBP: 79.8%). The IFX cohort had the older population (mean age, years [standard deviation]: 79.52 [11.01]), followed by the OBP (74.35 [10.88]) and OST (73.05 [10.67]). Baseline characteristics of each cohort are shown in Table 1. Baseline characteristics stratified by outcome for the development and validation data sets are provided in Supplemental Table S2*A–C*.

At 1-year follow-up, MACE IR (95% confidence interval [CI], in units of cases/1000 person-years) was 19.6 (18.5–20.7) in OST, 26.3 (25.4–27.1) in OBP, and 52.6 (50.7–54.5) in the IFX cohort (Fig. 2). IFX cohort also had the highest incidences when stratified by age groups (Supplemental Fig. S2). Those who experienced MACE were older in general (higher proportion aged >75 years) with higher comorbidity (Charlson score) and higher prevalence of drug use (eg, antihypertensives and beta-blockers).

Supplemental Fig. S3 display the IRs of 2-year MACE, 1- and 2-year stroke/MI, and MACE and stroke/MI outcomes stratified
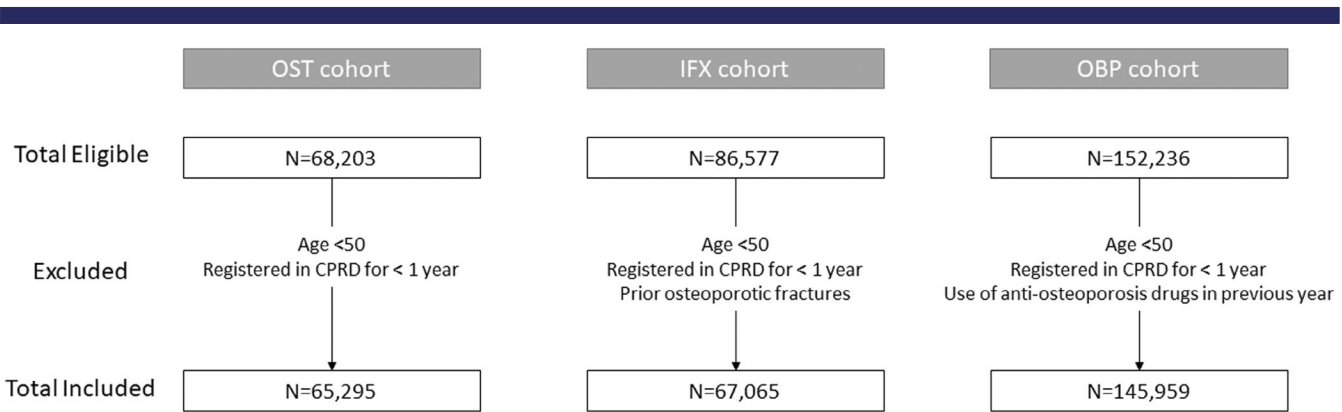
Fig. 1. Study flow chart. OST = patients with incident diagnosis of osteoporosis; IFX = patients with incident fragility fracture; OBP = incident users of oral bisphosphonates; CPRD = clinical practice research datalink.
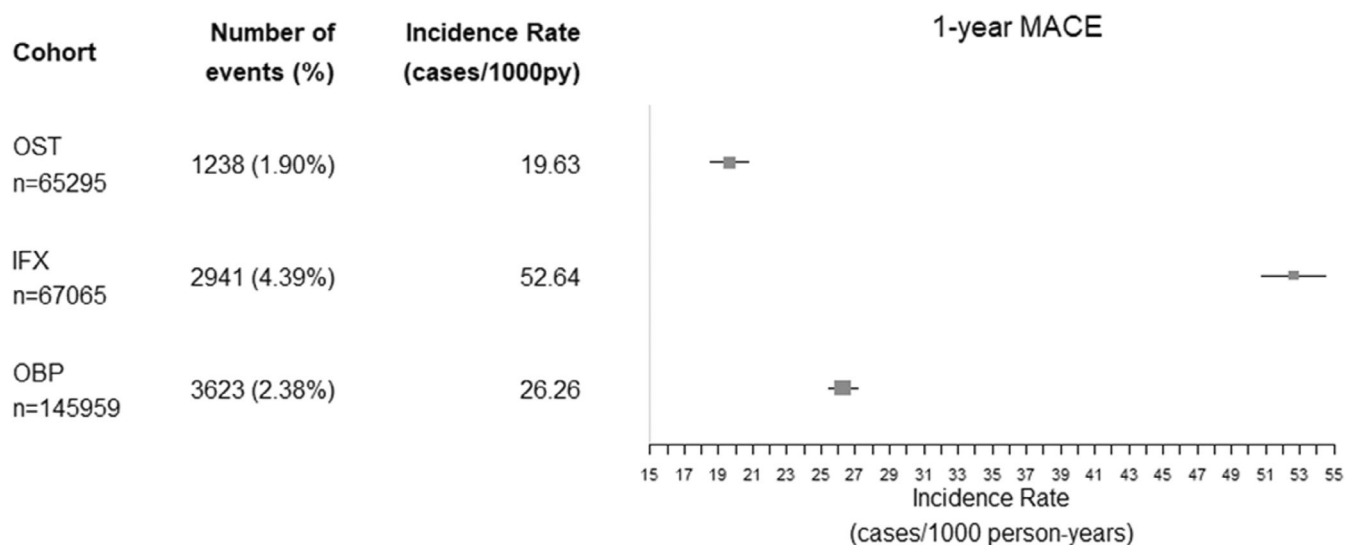
Fig. 2. Incidence rates of MACE after 1 year of follow-up. Incidence rate is reported with 95% confidence intervals. OST = patients with incident diagnosis of osteoporosis; IFX = patients with incident fragility fracture; OBP = incident users of oral bisphosphonates; MACE = composite outcome for the occurrence of either myocardial infarction, stroke, or cardiovascular disease death.

by sex. Overall, despite the considerably lower proportion of males in this study, they suffered higher incidence rates of both outcomes in the 1- and 2-year follow-up periods.

Development and performance of the prediction models

Predictive models using risk factors identified from lasso reach AUC values above 70% for the three models, and these equalled or outperformed the models using just QRISK factors (Supplemental Fig. S4). MACE models for OST and OBP populations had higher discrimination values compared with the stroke/MI models (Supplemental Fig. S5), whereas AUC values in IFX model were better for the stroke/MI outcomes. Differences between 1- and 2-year prediction models were minimal with no apparent pattern; however, sex-based models (Supplemental Fig. S5B, C) show lower AUC values for men-only models. It could be related to the considerably lower sample size of those cohorts.

Supplemental Figs. S6 and S7 report 1-year MACE calibration plots by age and by age and sex, respectively. Supplemental Figs. S8–S10 present the calibration plots of 2-year MACE and MI/stroke models. Generally, models were well-calibrated, with an overpredicting risk for the population <60 years old and underpredicting for those aged >80 years, probably caused by the lower proportion of participants belonging to either category.

Selected risk factors for patients at high risk of fracture

Table 2 displays the risk factors selected from lasso for the overall models of 1-year MACE along with their odd ratios (OR) and confidence intervals, and Supplemental Table S3 lists its beta coefficients. Sex, age, smoking, and drinking in the prior year, atrial fibrillation diagnosis, use of antihypertensive medication, prior MI or stroke, CVD history, number of concomitant medicines in

Table 2. Predictors of 1-Year MACE Overall Models (Risk Factors Selected by Lasso Regression)

Predictor	OST OR (95% CI)	IFX OR (95% CI)	OBP OR (95% CI)
Sex, male (%)	1.61 (1.3, 2)	1.29 (1.12, 1.49)	1.42 (1.25, 1.61)
Age group, years (%)			
50–59	Ref	Ref	Ref
60–69	1.36 (0.79, 2.35)	7.66 (3.05, 19.23)	1.58 (1.14, 2.19)
70–79	3.07 (1.85, 5.11)	12.56 (5.01, 31.5)	2.46 (1.79, 3.36)
80–89	4.9 (2.9, 8.28)	20.39 (7.84, 53)	4.26 (3.09, 5.87)
>89	7.88 (4.44, 13.99)	27.17 (9.92, 74.38)	5.79 (4.06, 8.24)
SES (%)	x	x	
1	x	x	Ref
2	x	x	1.17 (1.02, 1.36)
3	x	x	1.28 (1.11, 1.48)
4	x	x	1.34 (1.15, 1.56)
5	x	x	1.29 (1.08, 1.54)
Smoking[a]		x	
Ex	Ref	Ref	Ref
No	0.93 (0.73, 1.18)	1 (0.85, 1.18)	0.98 (0.79, 1.23)
Yes	1.42 (1.02, 1.98)	1.16 (0.89, 1.5)	1.14 (0.89, 1.47)
Drinking[a]			
Ex	Ref	Ref	Ref
No	1.19 (0.7, 2)	1.14 (0.85, 1.54)	1.03 (0.71, 1.49)
Yes	0.84 (0.51, 1.39)	1.11 (0.79, 1.57)	0.92 (0.65, 1.31)
Diabetes type I[b]	x	x	x
Diabetes type II[b]	x	x	1.11 (0.9, 1.36)
Chronic obstructive pulmonary disease[b]	x	x	1.05 (0.87, 1.27)
Chronic kidney disease[b]	x	x	0.81 (0.61, 1.06)
Rheumatoid arthritis[b]	x	x	0.88 (0.74, 1.04)
Lupus[b]	x	x	x
Systemic heart disease[a]	x	x	0.62 (0.37, 1.03)
Anti-osteoporosis use[a]	x	x	x
Heparin use[a]	x	x	x
Beta-blocker use[a]	x	1.11 (0.95, 1.29)	1.16 (1.02, 1.33)
Hypertension[a]	x	x	x
Deep vein thrombosis or pulmonary embolism[a]	x	x	x
Anticoagulant use[a]	x	x	0.93 (0.75, 1.14)
Antidepressants TCA[a]	x	x	x
Antidepressants SSRI[a]	x	x	1.28 (1.09, 1.49)
Hypercholesterolemia[a]	x	x	x
Statin use[a]	x	x	x
Osteoporosis history[b]	x	x	0.74 (0.66, 0.83)
Family history of cardiovascular disease	x	x	0.94 (0.78, 1.14)
Family history of cardiovascular disease before age 60 years	x	x	x
Heart failure[b]	x	x	1.03 (0.84, 1.27)
Migraine[b]	x	x	x
Severe mental illness[b]	x	x	x
Vascular disease[b]	x	x	x
Atrial fibrillation[b]	1.61 (1.27, 2.05)	1.2 (1.01, 1.43)	1.29 (1.08, 1.55)
On antihypertensive drug	1.23 (0.97, 1.55)	1.08 (0.87, 1.33)	1.05 (0.9, 1.22)
Antipsychotic use[a]	X	X	x
Steroid use[a]		X	x
Erectile dysfunction[a]	X	X	x
Charlson score	x		
0	x	x	Ref
1	x	x	1.01 (0.87, 1.17)
2	x	x	0.94 (0.79, 1.13)
≥3	x	x	1.06 (0.85, 1.31)
Cardiovascular disease	x	x	
No	x	x	Ref
Ever >1 year before index date	x	x	1.16 (1, 1.36)

(Continues)

Table 2. Continued

Predictor	OST OR (95% CI)	IFX OR (95% CI)	OBP OR (95% CI)
1 year before index	x	x	1.18 (0.84, 1.66)
6 months before index	x	x	1.52 (1.14, 2.03)
1 month before index	x	x	2.18 (1.49, 3.21)
MI or stroke			
No	Ref	Ref	Ref
Ever >1 year before index date	0.99 (0.7, 1.4)	1.23 (0.98, 1.55)	1.34 (1.09, 1.64)
1 year before index	2.03 (1.38, 2.99)	1.56 (1.19, 2.03)	2.52 (2, 3.18)
Established CVD[b]	1.9 (1.46, 2.48)	1.7 (1.42, 2.04)	1.49 (1.25, 1.79)
Any fracture history	x	x	x
No	x	x	x
Ever >1 year before index date	x	x	x
1 year before index	x	x	x
Hip fracture history	x	x	x
No	x	x	x
Ever >1 year before index date	x	x	x
1 year before index	x	x	x
Shoulder fracture history	x	x	x
No	x	x	x
Ever >1 year before index date	x	x	x
1 year before index	x	x	x
Spine fracture history	x	x	x
No	x	x	x
Ever >1 year before index date	x	x	x
1 year before index	x	x	x
Wrist fracture history	x	x	x
No	x	x	x
Ever >1 year before index date	x	x	x
1 year before index	x	x	x
BMI[a]		x	
<18.5	Ref	x	Ref
18.6–24.9	0.72 (0.49, 1.05)	x	0.74 (0.57, 0.96)
25–29.9	0.56 (0.35, 0.9)	x	0.58 (0.41, 0.81)
30–39.9	0.42 (0.2, 0.85)	x	0.55 (0.36, 0.84)
≥40	0.66 (0.22, 1.93)	x	0.39 (0.17, 0.91)
No. of GP visits[a]			
0	Ref	x	Ref
1–5	1.01 (0.61, 1.66)	x	0.9 (0.73, 1.1)
6–10	0.94 (0.56, 1.59)	x	0.78 (0.61, 1.01)
11–15	0.95 (0.55, 1.62)	x	0.78 (0.6, 1.01)
≥16	1.07 (0.63, 1.81)	x	0.86 (0.67, 1.12)
No. of GP emergency visits[a]	x		
0	x	Ref	Ref
1	x	1.25 (1.05, 1.47)	1.15 (0.99, 1.35)
2	x	1.43 (1.15, 1.78)	1.4 (1.13, 1.74)
3–5	x	1.21 (0.97, 1.5)	1.47 (1.2, 1.8)
≥6	x	1.13 (0.82, 1.56)	2.53 (1.96, 3.26)
eGFR[a]			
≤29	Ref	Ref	Ref
30–44	1.11 (0.44, 2.81)	0.87 (0.61, 1.24)	0.91 (0.56, 1.5)
45–59	0.89 (0.37, 2.15)	0.7 (0.38, 1.27)	0.83 (0.49, 1.4)
60–89	0.76 (0.31, 1.86)	0.59 (0.17, 2.01)	0.58 (0.27, 1.27)
≥90	0.79 (0.3, 2.07)	0.52 (0.13, 2.13)	0.5 (0.21, 1.22)
SBP[a]			
<120	Ref	Ref	Ref
120–139	1.19 (0.88, 1.61)	1.04 (0.85, 1.28)	1.09 (0.92, 1.31)
140–159	1.32 (0.98, 1.77)	1.2 (0.95, 1.51)	1.24 (1.02, 1.52)
≥160	1.32 (0.91, 1.89)	1.54 (1.11, 2.14)	1.39 (1.09, 1.77)

(Continues)

Table 2. Continued

Predictor	OST OR (95% CI)	IFX OR (95% CI)	OBP OR (95% CI)
DBP[a]	x		
<80	x	Ref	Ref
80–89	x	1.04 (0.89, 1.21)	0.94 (0.82, 1.08)
90–99	x	1.18 (0.91, 1.54)	1.05 (0.84, 1.31)
≥100	x	1.13 (0.71, 1.79)	1.31 (0.89, 1.93)
No. of concomitant medicines[a]			
0	Ref	Ref	Ref
1–3	0.69 (0.42, 1.12)	1.14 (0.9, 1.44)	0.87 (0.7, 1.07)
4–6	0.83 (0.51, 1.36)	1.29 (1.03, 1.63)	0.75 (0.59, 0.96)
7–9	1.01 (0.61, 1.66)	1.12 (0.87, 1.43)	0.88 (0.68, 1.14)
10–12	1.12 (0.67, 1.87)	1.26 (0.96, 1.65)	1 (0.76, 1.31)
≥13	1.11 (0.66, 1.88)	1.25 (0.95, 1.66)	0.98 (0.74, 1.31)
Cholesterol measurement[a] (HDL/LDL)		x	
≤3.5	Ref	Ref	Ref
3.6–5	1.34 (0.92, 1.95)	1.07 (0.56, 2.04)	1.2 (0.98, 1.46)
>5	1.74 (0.94, 3.2)	1.54 (0.38, 6.31)	1.35 (0.89, 2.03)
No. of previous fractures[b]			x
0	Ref	x	x
1	1.24 (1.01, 1.53)	x	x
≥2	0.99 (0.79, 1.25)	x	x

OST = patients with incident diagnosis of osteoporosis; IFX = patients with incident fragility fracture; OBP = incident users of oral bisphosphonates; OR = odds ratio; CI = confidence intervals; MACE = composite outcome for the occurrence of either myocardial infarction, stroke, or cardiovascular disease death; SES = socioeconomic status; MI = myocardial infarction; BMI = body mass index; eGFR = estimated glomerular filtration rate; SBP = cholesterol, systolic blood pressure; DBP = diastolic blood pressure.
[a]In the year before start.
[b]Ever.

the prior year, and estimated glomerular filtration rate (eGFR), systolic blood pressure (SBP), and cholesterol measurements in the prior year, appeared in all models. Predictors common in two of the three cohort models were body mass index (BMI), beta-blocker use, number of general practitioner (GP) visits, number of GP emergency visits, and diastolic blood pressure (DBP) measurements in the year before start.

Supplemental Table S4A, B summarizes risk factors selected from lasso and ORs for 2-year MACE and for MI/stroke models, respectively, and Supplemental Table S5A, B lists its beta coefficients. Supplemental Table S6A–C reports all sex-based models and Supplemental Table S7A–C lists its beta coefficients.

Detailed explanation and an example of how to obtain an estimate for an individual is reported in Supplemental Materials.

Discussion

In this study, we evaluated the incidence of major adverse cardiovascular events though a composite outcome, MACE,[44] and assessed risk factors of CVD to predict this outcome at 1 year in three different cohorts. The IFX cohort can be used for a secondary fracture prevention program, the OBP cohort has the potential to be used in primary prevention because it approximates patients newly diagnosed and treated for osteoporosis, and the OST cohort can be used as a general screening in primary care.

We observed that incidence of MACE was slightly higher at 1 year than at 2 years, especially for IFX cohort. When stratifying by sex, men had higher incidence rates than women, which agrees with results published by the British Health Foundation, where male incidences at UK in 2017 were higher than female.[45]

Prior studies using CPRD show that the general population aged 70+ years had an IR of MACE of 15.1 (per 1000 person-years),[32] whereas our study populations including younger individuals (ie, age 50+ patients) have higher IR. Specifically the IFX cohort had the highest incidence for MACE (51.1/1000 person-years), which could be explained by this cohort having an older age (71% were older than 75 years) and the largest proportion of men (23.3%) among the three cohorts, followed by OBP (26.3–20.2%) and OST (19.6–13.2%) cohorts. The observation of higher incidences in IFX cohort was consistent when IR of each study cohort was stratified by age groups.

Fitting the list of risk factors from QRISK into a prediction model for 1-year MACE events, we obtained AUC values of 0.73, 0.67, and 0.71 in OST, IFX, and OBP cohorts, respectively. However, starting from the list of "ALL" risk factors for CVD available in CPRD and selecting the most important through lasso regression, we obtained model equations that exceed QRISK (AUC in selected risk factors from ALL set: 0.75 in OST, 0.70 in IFX, and 0.75 in OBP). This list included generic features as well as those specific to the study population, and all of them can be found readily in primary care data. Among them, age had the largest statistically significant effect size.

Comparing our models to existing cardiovascular prediction tools, we found that the performances of Framingham and QRISK studies were higher in the general population: AUC >0.76 and >0.86, respectively.[5,11] Framingham equations have been validated and recalibrated multiple times using different populations,[46] whereas QRISK has a higher accuracy for UK population than the Framingham tool.[47] However, neither tool was developed for the osteoporotic/fracture risk population, and neither includes specific risk factors (eg prior fractures and alcohol consumption) for these particular patients, in whom short-term

cardiovascular risk might be over- or underestimated. In fact, Framingham only permits risk calculation over long periods, and there are no studies extrapolating to shorter risk intervals.

The need of specific CVD tools for populations at higher fracture risk and at short-term can be rationalised by the lower performance of the models using the QRISK list (ie, using the predictors selected for general population). This may be particularly interesting to note in our sensitivity analysis, which uses an outcome closer to the QRISK tool: AUC values of MI/Stroke models decrease to a range of 0.62 to 0.70 when applying the QRISK factors to osteoporotic/fracture risk population.

The proposed predictive models have good predictive power and internal validity (discrimination and calibration) in OBP and OST cohorts for 1-year MACE events (the obtained equations are included in this article), and the IFX models reach the 70% AUC threshold, considered as the minimum acceptable discrimination.[32]

Secondary and sensitivity analysis show no differences using 2-year models and better performance of MACE than MI/Stroke models.

The proposed study is observational in nature and hence cannot address causality but rather describe associations. There is no guarantee that all possible risk factors are included, but for all those factors that are, multivariable regression ensures that they are adjusted for (and hence reducing the risk of confounding). The three presented cohorts are not mutually exclusive but encompass the diversity of the population at high risk of fracture, and the different criteria used to evaluate them. Another limitation is the lack of external validity, which can be assessed in future studies to ensure the validity of the models across different populations. The enhanced performance observed in female population was expected due to the higher representation of females in our cohorts. The main strengths of this study are the large sample size and the wide selection of routinely collected potential risk factors included.[48]

To summarize, incidence rate of MACE events in the studied populations ranged from 19.6 to 52.6, with IFX as the cohort with the higher risk. Efforts in predicting the study events outline the differences between general and the osteoporotic/fracture risk population. The resulting algorithms include risk factors specific to the study population as well as more generic features that can be found easily in primary care data. Further work will focus on validating these models in external cohorts.

Disclosures

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Author Contributions

Marta Pineda-Moncusí: Writing – original draft; writing – review and editing. **Leena El-Hussein:** Formal analysis; writing – original draft; writing – review and editing. **Antonella Delmestri:** Data curation; writing – review and editing. **Cyrus Cooper:** Writing – original draft; writing – review and editing. **Alireza Moayyeri:** Conceptualization; writing – original draft; writing – review and editing. **Cesar Libanati:** Conceptualization; writing – original draft; writing – review and editing. **Emese Toth:** Conceptualization; writing – review and editing. **Sara Khalid:** Conceptualization; formal analysis; writing – original draft; writing – review and editing. **Daniel Prieto-Alhambra:** Conceptualization; writing – review and editing.

Peer Review

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Data Availability Statement

Data that supports the findings of this study was provided by UK CPRD database. Availability of data is subject to protocol approval by CPRD's Research Data Governance Process.

References

1. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke Statistics-2017 update: a report from the American Heart Association. Circulation. 2017;135(10):e146-e603.

2. NCD Countdown 2030 Collaborators. NCD countdown 2030: worldwide trends in non-communicable disease mortality and progress towards sustainable development goal target 3.4. Lancet. 2018; 392(10152):1072-1088.

3. Bhatnagar P, Wickramasinghe K, Wilkins E, et al. Trends in the epidemiology of cardiovascular disease in the UK. Heart. 2016;102(24): 1945-1952.

4. Svedbom A, Hernlund E, Ivergard M, et al. Osteoporosis in the European Union: a compendium of country-specific reports. Arch Osteoporos. 2013;8:137.

5. Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97(18):1837-1847.

6. Wilson PWF. Framingham risk score for hard coronary heart disease [Internet]. MDCalc. Available at: https://www.mdcalc.com/framingham-risk-score-hard-coronary-heart-disease2021

7. Andersson C, Johnson AD, Benjamin EJ, et al. 70-year legacy of the Framingham Heart Study. Nat Rev Cardiol. 2019;16(11):687-698.

8. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001;285(22):2864-2870.

9. Gage BF, van Walraven C, Pearce L, et al. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. Circulation. 2004;110(16):2287-2292.

10. Gage B. CHADS2 score for atrial fibrillation stroke risk [Internet]. MDCalc. Available at: https://www.mdcalc.com/chads2-score-atrial-fibrillation-stroke-risk2021

11. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. BMJ. 2017;357:j2099.

12. QRISK.org. QRISK®3–2018 risk calculator [Internet]. 2018. Available at: https://qrisk.org/three/

13. Garcia-Gomez MC, Vilahur G. Osteoporosis and vascular calcification: a shared scenario. Clin Investig Arterioscler. 2020;32(1):33-42.

14. Yedavally-Yellayi S, Ho AM, Patalinghug EM. Update on osteoporosis. Prim Care. 2019;46(1):175-190.

15. Tanko LB, Christiansen C, Cox DA, et al. Relationship between osteoporosis and cardiovascular disease in postmenopausal women. J Bone Miner Res. 2005;20(11):1912-1920.

16. Prieto-Alhambra D, Premaor MO, Fina Aviles F, et al. The association between fracture and obesity is site-dependent: a population-based study in postmenopausal women. J Bone Miner Res. 2012;27(2):294-300.

17. Premaor MO, Compston JE, Fina Aviles F, et al. The association between fracture site and obesity in men: a population-based cohort study. J Bone Miner Res. 2013;28(8):1771-1777.

18. Prieto-Alhambra D, Premaor MO, Aviles FF, et al. Relationship between mortality and BMI after fracture: a population-based study of men and women aged >/=40 years. J Bone Miner Res. 2014;29(8):1737-1744.

19. Martinez-Laguna D, Tebe C, Javaid MK, et al. Incident type 2 diabetes and hip fracture risk: a population-based matched cohort study. Osteoporos Int. 2015;26(2):827-833.

20. Collins TC, Ewing SK, Diem SJ, et al. Peripheral arterial disease is associated with higher rates of hip bone loss and increased fracture risk in older men. Circulation. 2009;119(17):2305-2312.

21. Laroche M, Pecourneau V, Blain H, et al. Osteoporosis and ischemic cardiovascular disease. Joint Bone Spine. 2017;84(4):427-432.

22. Sharma A, Einstein AJ, Vallakati A, et al. Risk of atrial fibrillation with use of oral and intravenous bisphosphonates. Am J Cardiol. 2014;113(11):1815-1821.

23. Huang BT, Huang FY, Gui YY, et al. Association between bisphosphonates therapy and incident myocardial infarction: meta-analysis and trial sequential analysis. J Cardiovasc Pharmacol. 2015;66(5):468-477.

24. Kranenburg G, Bartstra JW, Weijmans M, et al. Bisphosphonates for cardiovascular risk reduction: a systematic review and meta-analysis. Atherosclerosis. 2016;252:106-115.

25. EMA. Evenity (romosozumab). 2020. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/evenity

26. EMA. Clinical investigation of medicinal products for hormone replacement therapy of oestrogen deficiency symptoms in postmenopausal women. 2005. Available at: https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-hormone-replacement-therapy-oestrogen-deficiency-symptoms

27. EMA. Recommendation to restrict the use of Protelos / Osseor (strontium ranelate). 2013. Available at: https://www.ema.europa.eu/en/news/recommendation-restrict-use-protelos-osseor-strontium-ranelate

28. CPRD. Release notes: CPRD GOLD. 2018. Available at: https://cprdcw.cprd.com/_docs/Release_Notes_October2018.pdf

29. CPRD. Data highlights [updated page last reviewed March 29, 2021]. Available at: https://cprd.com/data-highlights. Accessed April 14, 2021.

30. Delmestri A, Prieto-Alhambra D. CPRD GOLD and linked ONS mortality records: reconciling guidelines. Int J Med Inform. 2020;136:104038.

31. Kanis, JA, Johansson H, Odén A, et al. "Characteristics of recurrent fractures." Osteoporosis International 2018;29(8):1747-1757.

32. Debray TP, Damen JA, Snell KI, et al. A guide to systematic review and meta-analysis of prediction model performance. BMJ. 2017;356:i6460.

33. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360(9349):1903-1913.

34. Lewington S, Whitlock G, Clarke R, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet. 2007;370(9602):1829-1839.

35. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111-188.

36. Jha P, Ramasundarahettige C, Landsman V, et al. 21st-century hazards of smoking and benefits of cessation in the United States. N Engl J Med. 2013;368(4):341-350.

37. Rosengren A, Smyth A, Rangarajan S, et al. Socioeconomic status and risk of cardiovascular disease in 20 low-income, middle-income, and high-income countries: the Prospective Urban Rural Epidemiologic (PURE) study. Lancet Glob Health. 2019;7(6):e748-e760.

38. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2014;25(10):2359-2381.

39. Pisani P, Renna MD, Conversano F, et al. Major osteoporotic fragility fractures: risk factor updates and societal impact. World J Orthop. 2016;7(3):171-181.

40. Barzilay JI, Davis BR, Pressel SL, et al. The impact of antihypertensive medications on bone mineral density and fracture risk. Curr Cardiol Rep. 2017;19(9):76.

41. Hofbauer LC, Henneicke H. β-Blockers and bone health. J Clin Invest. 2018;128(11):4745-4747.

42. Alexander LK LB, Ricchetti-Masterson K, Yeatts KB. Calculating person-time. ERIC Notebook. 2nd ed. Chapel Hill, NC: NCIPH Training Website, University of North Carolina; 2015. Available at: https://sph.unc.edu/files/2015/07/nciph_ERIC4.pdf. Accessed September 28, 2021.

43. Rubin DB. Underlying Bayesian theory. Multiple imputation for nonresponse in surveys. New York: John Wiley & Sons; 1987 pp 75-112.

44. Wilcox R, Kupfer S, Erdmann E. Effects of pioglitazone on major adverse cardiovascular events in high-risk patients with type 2 diabetes: results from PROspective pioglitAzone clinical trial in macro vascular events (PROactive 10). Am Heart J. 2008;155(4):712-717.

45. British Heart Foundation in collaboration with the Institute of Applied Health Research at the University of Birmingham. Heart and circulatory disease statistics 2020. Statistics Compendium (Tables). Available from: https://www.bhf.org.uk/what-we-do/our-research/heart-statistics/heart-statistics-publications/cardiovascular-disease-statistics-2020

46. Bitton A, Gaziano TA. The Framingham Heart Study's impact on global risk assessment. Prog Cardiovasc Dis. 2010;53(1):68-78.

47. Collins GS, Altman DG. An independent and external validation of QRISK2 cardiovascular disease risk score: a prospective open cohort study. BMJ. 2010;340:c2442.

48. Li Y, Sperrin M, Ashcroft DM, et al. Consistency of variety of machine learning and statistical models in predicting clinical risks of individual patients: longitudinal cohort study using cardiovascular disease as exemplar. BMJ. 2020;371:m3919.