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Fractures and their sequelae in non-dialysis-dependent chronic kidney disease: the Stockholm CREAtinine Measurement project

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ABSTRACT

Introduction. People undergoing maintenance dialysis are at high risk for fractures, but less is known about fracture incidence and associated outcomes in earlier stages of chronic kidney disease (CKD).

Methods. We conducted an observational analysis from the Stockholm Creatinine Measurement project, a Swedish health care utilization cohort during 2006–11. We identified all adults with confirmed CKD Stages 3–5 and no documented history of fractures and extracted information on comorbid history, ongoing medication, cardiovascular events and death. We studied incidence rates of fractures (overall and by location), with the estimated glomerular filtration rate (eGFR) as time-dependent exposure. We then studied hazard ratios [HRs and 95% confidence intervals (CIs)] for the events of death and major adverse cardiac events (MACE) using Cox regression with fracture as time-varying exposure.

Results. We identified 68 764 individuals with confirmed CKD (mean age 79 years, 56% women). During a median follow-up of 2.7 years, 9219 fractures occurred, of which 3105 were hip fractures. A more severe CKD stage was associated with a higher risk of fractures, particularly hip fractures: compared with CKD Stage 3a, the adjusted HR was 1.10 (95% CI 1.02–1.19), 1.32 (1.17–1.49) and 2.47 (1.94–3.15) for CKD Stage 3b, 4 and 5, respectively. Spline curves suggested a linear association with fracture risk with an eGFR <30 mL/min/1.73 m^2. Compared with non-fracture periods, incident fracture was associated with a 4-fold increased mortality within 90 days [HR 4.21 (95% CI 3.95–4.49)]. The risk remained elevated beyond 90 days [HR 1.47 (95% CI 1.40–1.54)] and was stronger after hip fractures. Post-fracture MACE risk was also highest in the first 90 days [HR 4.02 (95% CI 3.73–4.33)], particularly after hip fractures, and persisted beyond 90 days [HR 1.20 (95% CI 1.10–1.30)].

Conclusion. Our findings highlight the commonness of fractures and the increased risk for subsequent adverse outcomes in CKD patients. These results may inform clinical decisions regarding post-fracture clinical surveillance and fracture prevention strategies.

INTRODUCTION

Mineral and bone disorders (MBDs) are inherent in advanced chronic kidney disease (CKD), attributed to phosphate retention, disturbed calcium balance, vitamin D deficiency and secondary hyperparathyroidism [1]. These processes lead to derangements in bone turnover, mineralization and growth, resulting in reduced bone density and quality [2, 3], as well as cardiac hypertrophy, vascular calcification and arterial stiffness [4], particularly in end-stage kidney disease (ESKD) patients [5, 6]. Numerous studies have described an excess fracture risk in patients undergoing dialysis [7–14]. There are studies showing an excess fracture risk also in patients with CKD not on dialysis [8, 15–20], but evidence is mixed [17, 21, 22].

In ESKD, fractures have been associated with increased mortality [23, 24]. Health sequelae of fractures in earlier stages of CKD have been less studied. Previous studies have focused mostly on in-hospital and short-term mortality [8, 20, 25–28], leaving long-term mortality largely unexplored in CKD. Another plausible consequence of fractures is ischaemic cardiovascular disease (CVD), as recently suggested by general population studies [29–32]. We are not aware of studies evaluating the association between incident fractures and subsequent cardiovascular events in CKD patients, but we find this hypothesis conceivable given the features of CKD-MBD.

We aimed to comprehensibly characterize the incidence of fractures (overall and by location) in patients with manifest CKD Stages 3–5 not on dialysis in our region. We also explored sequalae of fractures, focusing on major adverse cardiovascular events (MACE) and death.

MATERIALS AND METHODS

Data source

The study population consisted of individuals drawn from the Stockholm Creatinine Measurement (SCREAM) project, a health care utilization cohort from the region of Stockholm, Sweden described in detail elsewhere [33]. In brief, SCREAM is a repository of all laboratory tests from any resident of Stockholm who had plasma or serum creatinine measured at least once during the years 2006–11. These lab tests were linked, via each citizen's unique personal identification number, to regional and national administrative databases with complete information on demographics, health care use, dispensed drugs, validated renal outcomes, diagnoses and vital status, with no loss to follow-up. The Regional Ethical Review Board in Stockholm approved the study; informed patient consent was not deemed necessary since all data were de-identified at the government's offices.

Participant selection and study design

For this observational study we included all adult (>18 years old) residents with confirmed CKD Stages 3–5, in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [34]. CKD was defined as having at least two consecutive outpatient creatinine measurements (>3 months and <2 years apart) indicating an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. The second measurement fitting this criterion was considered the index date. We then excluded participants with a history of fracture within 5 years before cohort entry and patients undergoing renal replacement therapy (RRT; as ascertained through linkage with the nationwide Swedish Renal Registry). A flow chart of the patient selection is depicted in Supplementary data, Figure S1.

This report contains two complementary study designs. First, we analysed incidence and fracture risk associated with eGFR. To minimize misclassification bias, eGFR was considered a time-dependent exposure using all subsequent eGFR determinations performed in outpatient health care. The outcome was the first encountered fracture. Second, we studied outcomes associated with incident fractures, with fractures considered a time-dependent exposure.

Study covariates

Study covariates included age, sex, laboratory values, comorbidities and concomitant medications. Comorbid conditions included hypertension, diabetes mellitus, ischaemic heart disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, cancer within 5 years prior to index, osteoporosis, arthritis, hypoparathyroidism, hyperparathyroidism, undernutrition, dementia, systemic inflammatory disease, chronic infections and psychoactive substance abuse, assessed using the International Classification of Diseases, Tenth Revision (ICD-10). Diagnostic codes are available since the implementation of ICD-10 in Sweden in 1997. Medications included renin–angiotensin–aldosterone system (RAAS) inhibitors, β-blockers, loop diuretics, statins, non-steroidal anti-inflammatory drugs (NSAIDs), vitamin D preparations, thiazides, opioids, anti-epileptic drugs, anti-depressants, corticosteroids, oestrogen supplementation, bisphosphonates and calcium salts. Information on drug dispensations was obtained from the Dispensed Drug Registry, a nationwide register with complete information on all prescribed drugs dispensed at Swedish pharmacies [35]. Drugs were assumed to be concomitant if there was a pharmacy dispensation at the time of or within the previous 5 months from index date or after 30 days. Covariate definitions are further detailed in Supplementary data, Tables S1 and S2.

Laboratory values considered were measurements of plasma creatinine ordered in outpatient care, performed with the enzymatic or corrected Jaffe method (alkaline picrate reaction), both methods being traceable to isotope dilution mass spectroscopy standards. Creatinine values <25 and >1500 µmol/L were considered implausible and were discarded. Plasma creatinine was used to estimate GFR with the Chronic Kidney Disease Epidemiology Collaboration equation [36]. The severity of

CKD was categorized as eGFR 45–59 mL/min/1.73 m^2 (CKD Stage 3a), 30–44 mL/min/1.73 m^2 (CKD Stage 3b), 15–29 mL/min/1.73 m^2 (CKD Stage 4) and <15 mL/min/1.73 m^2 (CKD Stage 5 not on renal replacement therapy; RRT).

Study outcomes and statistical analyses

In the first part, we assessed fracture risk across CKD Stages 3–5. We followed patients until the occurrence of the first fracture, ascertained through relevant ICD-10 codes (S12–S92 and M80, excluding fractures of the face and skull). We stratified by fracture location (hip and non-hip). To reduce the risk of CKD misclassification bias, eGFR was considered a time-dependent exposure and covariates were updated at each creatinine sampling. Patients were followed until death, emigration, start of RRT or the end of follow-up (31 December 2011). Restricted cubic spline models were used to better assess the multivariable adjusted association between eGFR (as a continuous variable) and the incidence of fractures.

In the second part we considered health events associated with incident fractures, using Cox regression with fractures as the time-dependent exposure. Thus a patient suffering a fracture during follow-up contributed with time to the fracture-free group before the event and thereafter to the fracture exposed group. Covariates were time updated at the time of incident fracture. We estimated multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) in fracture-exposed versus fracture-free periods for the events of death and MACE. Study outcomes were ascertained via linkage with the National Population Registry, with virtually no loss to follow-up for deaths or hospitalization diagnoses. MACE was defined as the composite of non-fatal ischaemic heart disease (I21, I22, I23, or I252), heart failure (I099, I110, I130, I132, I255, I420, I425-429, I43, I50), ischaemic stroke (H34.1, G45, G46, I60, I61, I63, I64) or death due to CVD (G45-46, H34.1, I00–I99). In the case of consecutive fractures, only the first one was considered for the time-updated exposure and the second was treated as a censoring event. To distinguish short-term versus long-term risk, we performed time-varying Cox regression analysis, splitting the follow-up of the exposed period in two intervals: <90 days and ≥90 days from incident fracture.

To evaluate the presence of residual confounding we included diverticulitis (K57) as a negative control outcome. Stratified analyses were performed to test the consistency of our results by age (<60 and ≥60 years), sex, presence/absence of diabetes mellitus or arthritis and eGFR strata (<30 or ≥30 mL/min/1.73 m^2).

Categorical data were expressed using frequency (%) and continuous data were expressed as median with interquartile range (IQR). Statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org). A two-sided P-value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

A total of 68 764 individuals with confirmed CKD Stages 3–5 met the inclusion criteria (Supplementary data, Figure S1).

The median follow-up time was 2.7 years (IQR 1.3–4.1) and the median number of creatinine measurements per patient was 4 (IQR 2–9).

The general characteristics of study participants at cohort entry are described in Table 1. Women constituted 56% of participants, with a median age of 79 years (IQR 71–85) and median eGFR of 51 (IQR 43–56) mL/min/1.73 m^2. Hypertension was the most common comorbidity, followed by congestive heart failure, cancer, diabetes mellitus and ischaemic heart disease. Consequently, RAAS inhibitors, β-blockers, loop diuretics and statins were the most frequently used medications. Bisphosphonate use was low and decreased with more severe CKD, while the use of vitamin D analogues increased. Generally age and common comorbidities increased with more severe CKD. Patient characteristics at the time of incident fracture are described in Supplementary data, Table S3. Briefly, patients who developed fractures seemed to be older, more often women, had more comorbidities and were more often using loop diuretics, opioids and calcium supplements.

Incidence of fractures and fracture types in CKD

A total of 9219 first fractures were registered, giving an overall incidence rate (IR) of 49/1000 person-years (PY). Of those, 3105 (34%, 17/1000 PY) were fractures of the hip and the remaining 6114 (66%, 33/1000 PY) were grouped as 'non-hip fractures'. Table 2 shows that the crude IR for all fractures and fracture subtypes increased in more severe CKD. Table 2 also describes HRs and 95% CIs for the risk of fracture associated with CKD stage. Compared with patients with CKD Stage 3a, the multivariable-adjusted risk of (any) fracture was significantly higher in patients with CKD Stage 4 [HR 1.20 (95% CI 1.11–1.29)] and CKD Stage 5 [HR 1.81 (95% CI 1.57–2.09)]. This increased risk was attributed to both hip and non-hip fractures, but the magnitude was greater for hip fractures [HR 1.10 (95% CI 1.02–1.19), 1.32 (1.17–1.49) and 2.47 (1.94–3.15) for CKD Stage 3b, 4 and 5, respectively]. Adjusted cubic splines (Figure 1) depict the multivariable-adjusted association between eGFR (as a continuous variable) and the risk of fractures, illustrating that the risk increases linearly when eGFR is ≤30 mL/min/1.73 m^2. The full Cox models are described in Supplementary data, Table S4. Generally, older patients, women and the presence of comorbidities such as dementia, CVD, chronic infection or cancer history were associated with a higher risk of fractures.

Subgroup analyses are detailed in Supplementary data, Table S5. Across CKD stages, the risk for hip fractures was marginally higher for men than for women (P for interaction = 0.049). No other interactions were observed.

Post-fracture outcomes

There were 18 993 deaths and 20 004 MACE registered during follow-up. Compared with fracture-free periods, incident fractures were associated with an increased risk of death in the short-term [<90 days, adjusted HR 4.21 (95% CI 3.95–4.49)] and after ≥90 days of follow-up [HR 1.47 (95% CI 1.4–1.54); Table 3]. Short- and long-term mortality was increased after both hip and non-hip fractures, but the risk was greater after a hip fracture.

Table 1. Baseline characteristics, overall and by CKD strata

Characteristics	Overall	CKD 3a	CKD 3b	CKD 4	CKD 5
Number of individuals	68 764	48 145	15 700	4213	706
Age (years), median (IQR)	79 (71, 85)	78 (71, 84)	82 (75, 87)	82 (73, 87)	75 (63, 84)
Women, n (%)	38 519 (56)	26 930 (56)	9048 (58)	2232 (53)	309 (44)
eGFR (mL/min/1.73 m^2), median (IQR)	51 (42–56)	54 (50–57)	39 (35–42)	25 (21–27)	11 (9–13)
Comorbidities, n (%)					
Hypertension	43 819 (64)	30 201 (63)	10 260 (65)	2853 (68)	505 (72)
Diabetes mellitus	15 137 (22)	10 059 (21)	3741 (24)	1108 (26)	229 (32)
Ischaemic heart disease	11 845 (17)	7467 (16)	3210 (20)	1029 (24)	139 (20)
Congestive heart failure	17 334 (25)	10 168 (21)	5227 (33)	1725 (41)	214 (30)
Peripheral vascular disease	6213 (9)	3865 (8)	1702 (11)	565 (13)	81 (12)
Cerebrovascular disease	11 989 (17)	7766 (16)	3190 (20)	908 (22)	125 (18)
Cancer	15 219 (22)	10 710 (22)	3435 (22)	923 (22)	151 (21)
Osteoporosis	3751 (5)	2608 (5)	851 (5)	240 (6)	52 (7)
Arthritis	2234 (3)	1662 (4)	438 (3)	111 (3)	23 (3)
Hypoparathyroidism	181 (0.3)	100 (0.2)	56 (0.4)	16 (0.4)	9 (1.3)
Hyperparathyroidism	660 (1)	401 (1)	181 (1)	68 (2)	10 (1)
Undernutrition	222 (0.3)	143 (0.3)	57 (0.4)	20 (0.5)	2 (0.3)
Dementia	3472 (5)	2240 (5)	936 (6)	256 (6)	40 (6)
Systemic inflammatory disease	4056 (6)	2782 (6)	947 (6)	284 (7)	43 (6)
Chronic infection	727 (1)	501 (1)	153 (1)	53 (1)	20 (3)
Psychoactive substance abuse	2316 (3)	1641 (3)	484 (3)	161 (4)	30 (4)
Ongoing medication, n (%)					
RAAS inhibitors	37 626 (55)	25 240 (52)	9297 (59)	2642 (63)	447 (63)
β-blockers	34 414 (50)	23 214 (48)	8436 (54)	2351 (56)	413 (59)
Loop diuretics	23 726 (35)	13 243 (28)	7283 (46)	2698 (64)	502 (71)
Statins	22 990 (33)	16 528 (34)	4926 (31)	1315 (31)	221 (31)
NSAIDs	11 602 (17)	8451 (18)	2528 (16)	574 (14)	49 (7)
Vitamin D preparations	1279 (2)	246 (0.5)	249 (2)	449 (11)	335 (48)
Thiazides	5543 (8)	3975 (8)	1302 (8)	249 (6)	17 (2)
Opioids	11 789 (17)	7872 (16)	2934 (18)	832 (20)	151 (21)
Anti-epileptic drugs	2194 (3)	1510 (3)	511 (3)	154 (4)	19 (3)
Antidepressants	9433 (14)	6461 (13)	2298 (15)	589 (14)	85 (12)
Corticosteroids	7439 (11)	5281 (11)	1610 (10)	485 (12)	63 (9)
Oestrogen supplementation	5781 (8)	4447 (9)	1075 (7)	237 (6)	22 (3)
Bisphosphonates	3415 (5)	2510 (5)	741 (5)	148 (4)	16 (2)
Calcium salts	8994 (13)	6089 (13)	1977 (13)	650 (15)	278 (39)

Compared with fracture-free periods, the short-term risk of MACE was significantly elevated after fracture occurrence [4.02 (95% CI 3.73–4.33)], particularly after a hip fracture [6.3 (95% CI 5.66–7)]. This risk persisted after 90 days. In contrast, no association was observed between fractures and our negative control outcome.

Subgroup analyses are detailed in Supplementary data, Tables S6 and S7. The association between hip fracture and mortality was stronger for men than women (P interaction = 0.01), for patients with eGFR >30 mL/min/1.73 m^2 versus <30 mL/min/1.73 m^2 (P interaction = 0.004), and for non-diabetics versus diabetics (P for interaction = 0.003). The association between incident fractures and MACE was also stronger for non-diabetics than for diabetics (P for interaction <0.001).

DISCUSSION

In this large, region-representative sample of patients with CKD Stages 3–5, we observed a gradual increase in (hip) fracture risk with lower eGFR, particularly with eGFR <30 mL/min/1.73 m^2. Incident fractures were associated with untoward sequelae such as increased risk of MACE and death, with risks being highest in the short term, but also extending beyond 90 days.

Our results are in agreement with some prior studies suggesting an excess risk of any fracture [15] and hip fracture [8, 18–21, 37] with lower eGFR. However, previous evidence may have had some limitations, such as the use of single eGFR measurements to define CKD, the inclusion of women only [17, 18], reliance on ICD diagnoses of CKD to identify cases [8], self-reports of comorbidities and medications or the inability to adjust for these important confounders [15, 16, 18, 19, 21, 25, 26]. Some studies excluded pathological fractures from their analysis [8, 25] and others adjusted for bone mineral density [17], which may lie within the causal pathway. This may have altogether underestimated the true fracture burden. Elliot *et al.* [38] found no relationship between eGFR and fracture incidence in a large Canadian health care–based study, possibly explained by a less rigid CKD definition (single GFR estimation) and by the use of eGFR >90 mL/min/1.73 m^2 as a reference. The inaccuracies of creatinine-based eGFR, particularly among the elderly affected by comorbidities, frailty and muscle debilitating conditions, may have obscured the association if these individuals with inaccurately high eGFR are considered referent. This study and ours coincide, however, in the observation of an increased fracture

Table 2. IRs and HRs for fractures in relation to CKD severity stages

CKD stage	No. of fractures	IR per 1000 PY (95% CI)	Adjusted[a] HR (95% CI)	Adjusted[b] HR (95% CI)	Adjusted[c] HR (95% CI)
Any fracture (*n* = 9219), IR 49 (95% CI 48.4–50.5) per 1000 PY					
CKD 3a	5446	45.4 (44.2–46.7)	1	1	1
CKD 3b	2693	54.4 (52.3–56.4)	1.20 (1.14–1.25)	1.04 (0.99–1.09)	1.01 (0.96–1.06)
CKD 4	888	64.3 (60.2–68.6)	1.41 (1.31–1.52)	1.27 (1.18–1.37)	1.20 (1.11–1.29)
CKD 5	192	59.2 (51.4–67.9)	1.29 (1.12–1.50)	1.89 (1.64–2.18)	1.81 (1.57–2.09)
Hip fractures (*n* = 3105), IR 17 (95% CI 16.1–17.2) per 1000 PY					
CKD 3a	1671	13.9 (13.3–14.6)	1	1	1
CKD 3b	1017	20.5 (19.3–21.8)	1.47 (1.36–1.60)	1.15 (1.06–1.24)	1.10 (1.02–1.19)
CKD 4	345	25.0 (22.5–27.7)	1.79 (1.59–2.02)	1.41 (1.25–1.59)	1.32 (1.17–1.49)
CKD 5	72	22.2 (17.6–27.6)	1.59 (1.26–2.02)	2.59 (2.04–3.29)	2.47 (1.94–3.15)
Other fractures (*n* = 6114), IR 33 (95% CI 32.0–33.6) per 1000 PY					
CKD 3a	3775	31.5 (30.5–32.5)	1	1	1
CKD 3b	1676	33.8 (32.3–35.5)	1.07 (1.01–1.14)	0.99 (0.93–1.05)	0.96 (0.90–1.02)
CKD 4	543	39.3 (36.1–42.7)	1.24 (1.13–1.36)	1.18 (1.08–1.29)	1.12 (1.02–1.23)
CKD 5	120	37.0 (31.0–43.9)	1.16 (0.97–1.39)	1.56 (1.30–1.87)	1.50 (1.25–1.80)

[a]Adjusted for age and sex.
[b]Adjusted for Model 1 plus comorbidities: hypertension, diabetes mellitus, ischaemic heart disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, cancer, osteoporosis, arthritis, hypoparathyroidism, hyperparathyroidism, undernutrition, dementia, systemic inflammatory disease, chronic infection and psychoactive substance abuse.
[c]Adjusted for Model 2 plus ongoing medication: RAAS inhibitors, β-blockers, loop diuretics, statins, NSAIDs, vitamin D, thiazides, opioids, anti-epileptic drugs, antidepressants, corticosteroids, oestrogen supplementation, bisphosphonates and calcium supplements.

incidence when eGFR is <30 mL/min/1.73 m^2, which is the range where CKD-MBD alterations become clinically manifest [11].

A novelty is our analysis of health events following incident fractures. Using fractures as time-dependent exposure allowed us to dissect short- and long-term risks, considering the background event risk in non-exposed periods. We confirm previous studies showing an increased short-term death risk in patients with fractures [8, 25–28] and add novel evidence of a long-term risk. This association was somehow expected for hip fractures [39, 40], but was not reported before for 'minor fractures'.

Interestingly, in our interaction analysis, we observed a stronger association between CKD and fractures in men than women, which agrees with previous findings of a stronger risk of vertebral fractures in men undergoing haemodialysis [41]. We also observe a stronger association between incident hip fractures and mortality in men. We are not aware of studies of CKD patients reporting such sex differences, which needs to be confirmed in further investigations. Because previous reports have focused on women, or on patients with a history of fractures, men may have been underrepresented or died before they could be included in previously investigated cohorts. Nonetheless, such findings are also consistent with recent epidemiological data from the UK general population demonstrating greater post-fracture mortality in men [42]. Our multivariable analyses (Supplementary data, Table S4) also illustrate the multiple conditions associated with fracture risk in this multimorbid and complex population, including diabetes, cardiovascular comorbidity or, as evidenced by earlier reports [43], the presence of dementia.

The observed association between incident fractures and MACE in CKD is novel in nephrology but is in line with recent evidence in the general population indicating a bidirectional relationship between CVD and poor bone health [29–31, 44, 45].

A recent meta-analysis found consistency across published studies with regard to CVD risk in patients with low (versus high) bone mineral density [pooled HR 1.33 (95% CI 1.27–1.38)] or a history of fractures [HR 1.25 (95% CI 1.05–1.48)] [45]. The underlying mechanisms remain inadequately elucidated, but this association is consistent with the observation in haemodialysis populations that the prevalence of vertebral fractures assessed by quantitative morphometry is strongly associated with vascular calcifications [41]. Osteoporosis and CVD share risk factors, such as a lack of physical activity, smoking, low-grade inflammation, alcohol use, glucocorticoid use and diabetes [45, 46]. In renal insufficiency, CKD-MBD leads, on the one hand, to arterial stiffness, vascular calcification and cardiac hypertrophy and, on the other hand, to heightened bone turnover, loss of bone quality and susceptibility to fragility fractures [1, 2, 4, 47, 48]. Therefore the observed associations may solely reflect the presence of such common risk factors. The increased cardiovascular risk could also relate to complications of the fractures *per se*, such as immobility, surgical procedures, nosocomial infections and a more liberal use of NSAIDs.

Compared with previous reports, our analysis offers some methodological strengths, starting with complete regional coverage by a single health care provider and universal health care access. The identification of CKD patients with two consecutive eGFR measurements and the use of eGFR as a time-dependent exposure reduces misclassification bias. We did not exclude pathological fractures, since CKD-induced fractures are, by nature, pathological, and we evaluated all incident fractures except for those of the skull and face (viewing them as more associated with trauma than to underlying bone disease), thereby providing a more comprehensive characterization of the burden of fractures in CKD. Our study also has limitations, including our inability to infer causality and the lack of information on important confounders such as albuminuria, body mass index, smoking or alcohol use and the lack of biomarkers such as
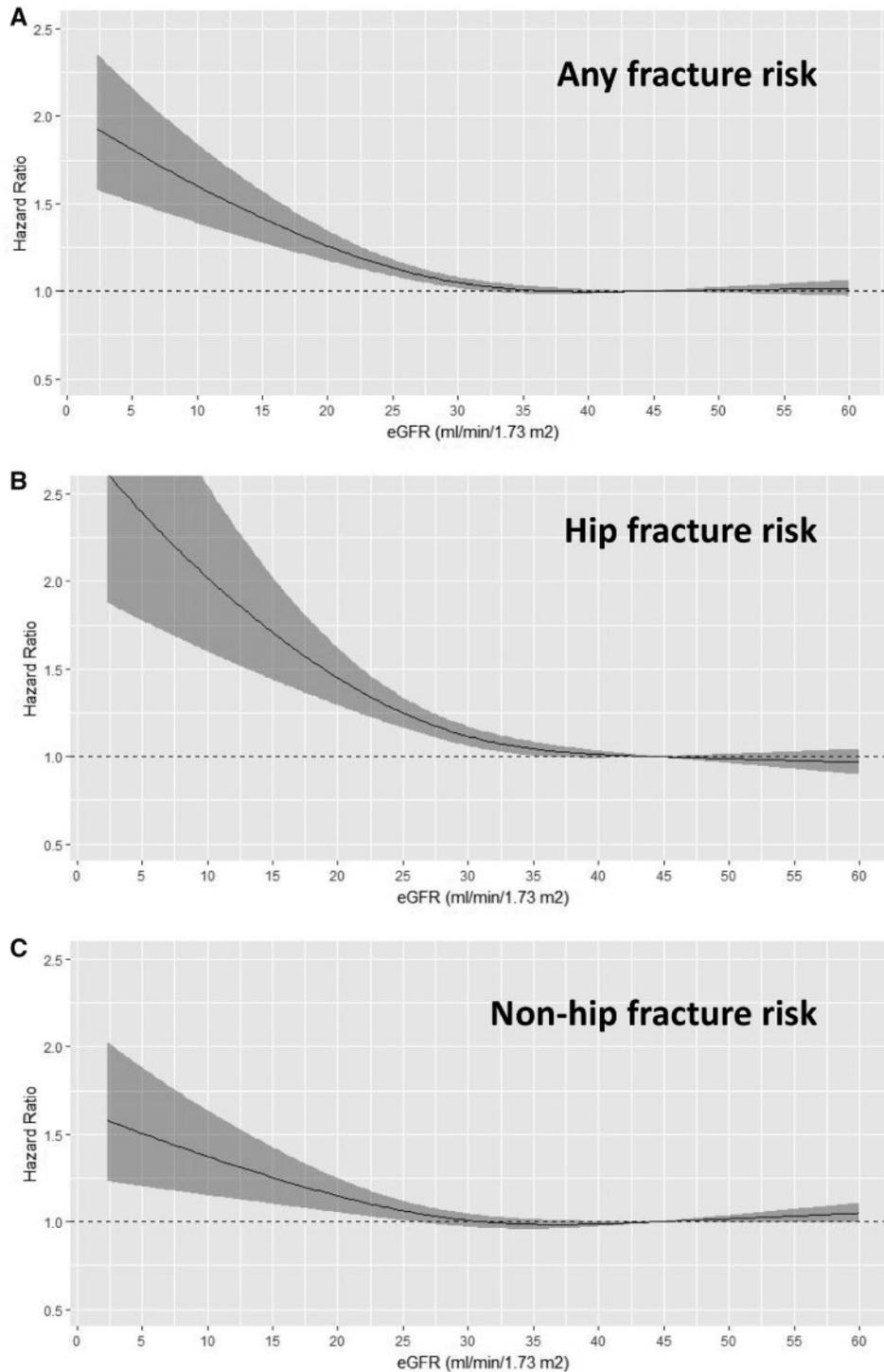
FIGURE 1: Restricted cubic splines showing multivariable-adjusted HRs (95% CI) for any **(A)** fracture, **(B)** hip fracture and **(C)** non-hip fractures across eGFRs (continuous). Covariate adjustments as in Table 2, Model 3.

alkaline phosphatase, 25-hydroxy vitamin D or parathyroid hormone (PTH). Nonetheless, our negative control outcome analysis suggests a potentially low risk of residual confounding.

Even if our observations mainly reflected underlying morbidity, they highlight the commonness of fractures and the susceptibility for adverse outcomes in CKD patients and thereby emphasize the need for fracture prevention and post-fracture clinical surveillance. Implementation of the fracture risk

assessment tool has recently been shown to predict major osteoporotic fractures and hip fractures in CKD patients not on dialysis with equal accuracy irrespective of kidney function [49, 50]. The 2017 updated KDIGO guidelines recommend bone density assessment for all CKD patients [11, 51]. KDIGO also recommends the use of bisphosphonates for osteoporosis patients with CKD G3a-G3b who have normal PTH and a high risk of fractures [11, 51]. We note a small proportion of patients with

Table 3. Incident fractures and risk of subsequent adverse events before and after 90 days

Event	Number of events	Non-fracture periods	<90 days after fracture			≥90 days after fracture		
		Event rate (per 1000 PY)	Event rate (per 1000 PY)	Crude HR (95% CI)	Adjusted HR (95% CI)	Event rate (per 1000 PY)	Crude HR (95% CI)	Adjusted HR (95% CI)
Incident fracture (any)								
Death	18 993	84	553	6.6 (6.2–7.0)	4.2 (4.0–4.5)	176	2.1 (2.0–2.2)	1.5 (1.4–1.5)
MACE	20 004	109	544	5.2 (4.9–5.6)	4.0 (3.7–4.3)	138	1.5 (1.4–1.6)	1.2 (1.1–1.3)
Incident hip fracture								
Death	17 150	84	961	11.5 (10.6–12.5)	5.9 (5.4–6.4)	248	3.0 (2.8–3.2)	1.7 (1.5–1.8)
MACE	18 703	109	991	9.6 (8.7–10.6)	6.3 (5.7–7.0)	163	1.8 (1.6–1.9)	1.2 (1.1–1.3)
Incident non-hip fracture								
Death	17 504	84	364	4.3 (4.0–4.8)	3.09 (2.8–3.4)	148	1.8 (1.7–1.9)	1.4 (1.3–1.4)
MACE	19 143	109	360	3.5 (3.1–3.8)	2.9 (2.6–3.2)	129	1.4 (1.3–1.5)	1.2 (1.1–1.3)
Negative control outcome								
Diverticulitis	2931	15	20	1.4 (1.0–1.9)	1.3 (0.9–1.8)	13	1.0 (0.8–1.2)	0.9 (0.8–1.1)

Adjusted for age, sex, eGFR, hypertension, diabetes mellitus, ischaemic heart disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, cancer, osteoporosis, arthritis, hypoparathyroidism, hyperparathyroidism, undernutrition, dementia, systemic inflammatory disease, chronic infection and psychoactive substance abuse.

CKD Stage 3 in our study using bisphosphonates, possibly suggesting underuse. Conversely, we also note a small proportion of patients with CKD Stages 4–5 using bisphosphonates, which may indicate off-label use. Other pharmacological treatments, such as osteoblast-stimulating agents, are also often discouraged in advanced CKD [52]. Of late, denosumab, a biologically active osteoclast inhibitor, has appeared as a new prevention tool for selected CKD patients [11]. Fall preventive efforts seem called for, particularly among the elderly, as well as counselling on physical activity to increase muscle strength, improve bone resistance and ameliorate cardiovascular fitness. Efforts towards phosphate, calcium and PTH control, together with supplementation of vitamin D, surely play a role, but we are not aware of strong evidence that this is the case.

In summary, the risk of fractures in non-dialysis-dependent CKD patients increased gradually with lower kidney function. The occurrence of fractures was associated with untoward, sometimes fatal sequalae, in the form of MACE and death, both in the immediate 90-day period and thereafter. Although our observations need to be confirmed in independent cohorts, we find it reasonable to propose that CKD patients suffering fractures should be closely monitored for signs and symptoms of cardiovascular complications and be (re-)evaluated for CVD prevention.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

CONFLICT OF INTEREST STATEMENT

B.L. is employed by Baxter Novum.

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