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ORIGINAL ARTICLE

The risk of new fragility fractures in patients with chronic kidney disease and hip fracture—a population-based cohort study in the UK

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Abstract

Summary Chronic kidney disease (CKD) is a risk factor for fractures. However, in hip fracture patients, CKD G3-G5 was associated with a higher mortality risk and not associated with a higher risk of subsequent non-hip fractures compared to eGFR > 60 ml/min. The higher mortality risk may, as competing risk, explain our findings.

Introduction Chronic kidney disease (CKD) is a known risk factor for fragility fractures. Patients aged 50+ with a recent fragility fracture have an increased risk of subsequent fractures. Our aim was to evaluate the association between CKD stages G3–G5 versus estimated glomerular filtration rate (eGFR) > 60 ml/min and the risk of a new non-hip fracture or fragility fracture in patients with a first hip fracture.

Methods Population-based cohort study using the UK general practices in the Clinical Practice Research Datalink. Associations between CKD stage and first subsequent fracture were determined using Cox proportional hazard analyses to estimate hazard ratios (HRs). To explore the potential competing risk of mortality, cause-specific (cs) HRs for mortality were estimated.

Results CKD G3–G5 was associated with a lower risk of any subsequent non-hip fracture (HR: 0.90, 95%CI: 0.83–0.97), but not with the risk of subsequent major non-hip fragility fracture. CKD G3-G5 was associated with a higher mortality risk (cs-HR: 1.05, 95%CI: 1.01–1.09). Mortality risk was 1.5- to 3-fold higher in patients with CKD G4 (cs-HR: 1.50, 95%CI: 1.38–1.62) and G5 (cs-HR: 2.93, 95%CI: 2.48–3.46) compared to eGFR > 60 ml/min.

Conclusions The risk of a subsequent major non-hip fragility fractures following hip fracture was not increased in patients with CKD G3–G5 compared to eGFR > 60 ml/min. Mortality risk was higher in both hip fracture and non-hip fracture patients with CKD G4 and G5. The higher mortality risk may, as competing risk, explain our main finding of no increased or even decreased subsequent fracture risk after a hip fracture in patients with CKD G3–G5.

Keywords Bone · Chronic renal failure · Fragility fracture · Renal disease

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Introduction

Chronic kidney disease (CKD) is a known risk factor for fragility fractures, in particular the first fragility fracture [1–6]. Previous research has shown that CKD (an estimated glomerular filtration rate (eGFR) of < 60 ml/min) is associated with an increased prevalence of hip fractures [2]. This was confirmed by a cross-sectional study among German elderly ($n = 5313$) which showed that an eGFR < 65 ml/min was associated with increased risk of fractures of the femur, vertebrae and radius [3]. It was shown that CKD G3a and G3b were associated with an increased risk of any type of fracture as compared to CKD G1-G2 in both men and women [6]. In men with CKD stage G4, the risk of hip fracture was found to be increased compared with men with a normal renal function [5]. Further, in patients with end-stage renal disease, it was reported that both women and men had a relative risk of 4.4 for sustaining a hip fracture as compared with people of the same sex in the general population [4].

Patients aged 50 years and older who recently sustained a fragility fracture are at increased risk of subsequent fractures [7–10]. This subsequent fracture risk is the highest following hip fractures and clinical vertebral fractures [8]. An excess fracture-related mortality risk in patients aged 60–80 years with a minimal trauma fracture was demonstrated by Bliuc et al. [11], with the highest post-fracture mortality after a hip fracture [11, 12].

So far, published studies have investigated the association between CKD and the risk of a first fragility fracture. However, the association between CKD and subsequent fracture risk is unknown. Therefore, the objectives of this study were to evaluate the association between CKD (stages G3–G5 versus eGFR > 60 ml/min) and the risk of a subsequent major non-hip fragility fracture (humerus, distal forearm and vertebral fracture) or any non-hip subsequent fracture in patients with a first hip fracture.

Materials and methods

Source population

Data for this study were obtained from the Clinical Practice Research Datalink (CPRD) GOLD in the United Kingdom (UK), previously known as the General Practice Research Database (GPRD) [www.CPRD.com]. The CPRD GOLD contains computerised medical records of 674 primary care practices in the UK, representing 6.9% of the UK population. The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions, and major outcomes since 1987, with ongoing data collection [13]. Previous studies using CPRD data have shown to be highly valid, with for example for hip fractures over 90% confirmed diagnoses [14]. CPRD GOLD had a high quality of recording of all-cause mortality [15].

Study population

We conducted a retrospective population-based cohort study. The study population consisted of all patients aged ≥ 50 at start of follow-up with a first hip fracture during the period of valid CPRD data collection. For this study, data collection started in April 2004 (i.e. when the Quality and Outcomes Framework (QOF) was introduced) and ended in December 2016. Patients with a hip fracture were matched by sex, year of birth (maximum difference of 5 years) and practice to up to two control patients without a hip fracture using incidence density sampling. The index date was set to the date of the first record of a hip fracture. The index date of controls was set to the index date of their matched hip fracture patient. There was a lead-in period of 1 month after the hip fracture date in order to avoid any delayed recording of fractures that occurred at the index date. Patients with records of unspecified fracture types before the index date were excluded. Patients were followed from the index date until the end of data collection, date of transfer of the patient out of the practice, the patient's death or outcome of interest, whichever came first. Patients with a history of a kidney transplantation before the index date were excluded.

Exposure and outcome

The eGFR was assessed in a time-dependent manner. Follow-up time in both cohorts was divided into 90-day intervals. For all patients, the most recently recorded renal function assessed in the time period ranging from 1 week to 1 year before the start of an interval was evaluated. Renal function was estimated by using the recorded laboratory test data. The reported eGFR or, if only a serum creatinine measurement was available, the Modification of Diet in Renal Disease (MDRD) formula was used to calculate eGFR values, according to the methods by Eppenga et al. [16]. In the event of multiple eGFR values on the same day, the mean value was used. The "Kidney Disease: Improving Global Outcomes" (KDIGO) classification for CKD consists of five stages: G1: eGFR > 90 ml/min/1.73 m^2, G2: eGFR 60–89 ml/min/1.73 m^2, G3: eGFR 30–59 ml/min/1.73 m^2, G4: eGFR 15–29 ml/min/1.73 m^2 and G5: eGFR < 15 ml/min/1.73 m^2 [17]. Follow-up time was stratified into three levels: eGFR ≥ 60 ml/min and eGFR < 60 ml/min (stages G3, G4 and G5 CKD) according to KDIGO, and an unknown eGFR value. We did not use Read codes from the clinical and referral files, which contain numerical CKD categories, since there is evidence of

miscoding of the CKD codes compared with biochemically confirmed CKD [18]. As a result of this classification, patients' exposure time could move between different CKD groups during follow-up. We studied the following outcomes: the first subsequent major non-hip fragility fracture, the first subsequent non-hip fracture (including non-fragility fractures) and all-cause mortality. Fractures were classified using Read codes.

Potential confounders

The presence of risk factors for fracture and subsequent fracture was assessed by reviewing computerised medical records for any record of a risk factor prior to the start of an interval. The following potential confounders were considered at baseline: sex, smoking status (non-smoker, current smoker, former smoker or unknown), alcohol use (yes, no, unknown) and body mass index (BMI) (< 25.0, 25.0–29.9, ≥ 30 kg/m^2 or unknown). Additionally, the use of any of the following drugs in the 6 months before the start of an interval was considered as a potential confounder: corticosteroids (systemic and inhaled), benzodiazepines, other sedatives and hypnotics, anti-Parkinson drugs, antipsychotics, antidepressants, narcotic analgesics stronger than tramadol, anticonvulsants, diuretics, renin-angiotensin-aldosterone-system (RAAS) inhibitors and drugs used for the treatment of diabetes. Also, anti-osteoporosis treatments were considered as potential confounders: bisphosphonates, denosumab, strontium ranelate, calcitonin and parathyroid hormone (PTH), hormone replacement therapy (HRT), and selective estrogen receptor modulators (SERMs) and finally, vitamin D and calcium.

Other potential confounders were determined at the start of each new time interval: age, a history of a major (non-hip) fracture, inflammatory bowel disease (Crohn's disease and ulcerative colitis), rheumatoid arthritis, a history of falls (in the 7–12 months before the start of an interval) and the presence of secondary osteoporosis in accordance with the fracture risk assessment tool (FRAX) definition [anorexia nervosa, coeliac disease, type 1 diabetes mellitus, hypogonadism, osteogenesis imperfecta, osteomalacia, liver disease (cirrhosis, hepatitis and neoplasms), malnutrition, mal-absorption and premature menopause].

Statistical analysis

Cox regression analysis (SAS 9.4. PHREG procedure) was used for the primary comparison to estimate the association of normal versus reduced renal function (eGFR < 60 vs. eGFR ≥ 60) and the risk of a subsequent non-hip major osteoporotic fracture and the risk of any (non-hip) fracture after a hip fracture, expressed as hazard ratios (HRs) with 95% confidence intervals (95%CI). Analyses were stratified by sex, age and CKD stages. CKD stage 5 was further stratified by history of dialysis. Confounders were entered into the final model if they independently changed the beta coefficient of the association between renal function and subsequent fracture by at least 5% and/or when consensus about inclusion existed within the team of researchers, supported by clinical evidence from literature. The Wald test was used to test the statistical differences between the CKD groups.

Since we performed time-dependent analyses, we were not able to perform the fine and gray adjustments to study mortality as potential competing risk [19]. Therefore, we estimated the cause-specific (cs)-HRs for mortality (i.e. follow-up time was not only censored on end of valid data collection, but also on the occurrence of any or major osteoporotic fracture). Further, the cumulative incidence of different outcomes (subsequent fracture and alive, subsequent fracture and death, death, alive and no subsequent fracture) after the initial hip fracture was calculated based on the paper by Bliuc et al. [20]. Missing data were handled as a separate category in the regression models.

Sensitivity analyses

In a sensitivity analysis, we studied the association between renal function and the risk of a first major non-hip osteoporotic fracture (humerus, distal forearm and vertebral fracture) and any non-hip fracture in the control cohort (non-hip fracture cohort). We also studied the risk of mortality in the non-hip fracture cohort. The cumulative incidence of different outcomes (major osteoporotic fracture (MOF) and alive, MOF and death, death, alive and no MOF) was calculated in the non-hip fracture cohort as well. Further, we preformed two additional sensitivity analyses in high-risk patients. We selected patients who had a history of falling or a history of a fragility fracture at baseline and investigated the association between kidney function and risk of fracture in those two study populations. Moreover, we estimated the risk of fracture and all-cause mortality in the first year and second year after the index date in both the hip fracture population and in the non-hip fracture cohort. The study was approved by the Independent Scientific Advisory Committee for MHRA database research, protocol 17_260R2.

Results

The hip fracture cohort consisted of 37,820 patients. At baseline, the CKD classification of 23,780 patients was known: 13,047 had an eGFR > 60 ml/min and 10,733 had CKD stages G3–G5. The control population comprised 74,440 patients in total. The reasons for exclusion are shown in the flowcharts of the hip fracture cohort and matched controls (Supplemental Fig. 1). Baseline characteristics of both the hip fracture cohort and the control cohort are shown in Table 1. In the group of

Table 1 Baseline characteristics

	Patients with a hip fracture				Patients without a hip fracture			
	eGFR > 60 ml/min		CKD stages G3–G5		eGFR > 60 ml/min		CKD stages G3–G5	
Characteristic	*N* = 13,047	%	*N* = 10,733	%	*N* = 25,072	%	*N* = 19,511	%
Mean Follow-up time (SD) (years)	3.2	2.9	2.8	2.8	4.3	3.1	4.1	3.1
Median Follow-up time (IQR) (years)	2.4	4.2	1.8	3.8	3.7	4.6	3.3	4.6
Sex								
Men	3945	30.2	2540	23.7	7697	30.7	4193	21.5
Women	9102	69.8	8193	76.3	17,375	69.3	15,318	78.5
Age								
Mean age (SD, years)	79.2	9.7	84.2	7.5	79.0	9.5	84.1	6.9
50–59 years	588	4.5	64	0.6	1056	4.2	80	0.4
60–69 years	1609	12.3	387	3.6	3070	12.2	581	3.0
70–79 years	3610	27.7	2033	18.9	7265	29.0	3696	18.9
80–89 years	5571	42.7	5648	52.6	10,922	43.6	10,804	55.4
90+ years	1669	12.8	2601	24.2	2759	11.0	4350	22.3
Body mass index								
Mean (SD, kg/m^2)	25.3	4.6	26.1	4.7	26.39	4.7	26.86	4.7
< 18 kg/m^2	406	3.1	186	1.7	300	1.2	187	1.0
18–24.9 kg/m^2	5725	43.9	4068	37.9	9513	37.9	6462	33.1
25–29.9 kg/m^2	4113	31.5	3657	34.1	9422	37.6	7435	38.1
30–34.9 kg/m^2	1291	9.9	1264	11.8	3329	13.3	2930	15.0
≥ 35 kg/m^2	356	2.7	408	3.8	1112	4.4	1004	5.1
Missing	1156	8.9	1150	10.7	1396	5.6	1493	7.7
Smoking status								
Non-smoker	4490	34.4	3970	37.0	9316	37.2	7492	38.4
Ex-smoker	6412	49.1	5637	52.5	13,457	53.7	10,701	54.8
Current smoker	2042	15.7	1009	9.4	2201	8.8	1218	6.2
Missing	103	0.8	117	1.1	98	0.4	100	0.5
Alcohol use								
Yes	7513	57.6	5568	51.9	16,141	64.4	11,049	56.6
No	4362	33.4	4057	37.8	7415	29.6	6984	35.8
Missing	1172	9.0	1108	10.3	1516	6.0	1478	7.6
Disease history								
Fragility fracture[a]	2588	19.8	2195	20.5	2900	11.6	2580	13.2
Falling (7–12 months prior index date)	783	6.0	685	6.4	773	3.1	729	3.7
Secondary osteoporosis[b]	785	6.0	643	6.0	957	3.8	806	4.1
Inflammatory bowel disease[c]	212	1.6	168	1.6	286	1.1	228	1.2
Rheumatoid arthritis	631	4.8	429	4.0	798	3.2	526	2.7
Cancer (excluding nonmelanoma skin cancers)	4293	32.9	3322	31.0	8123	32.4	5946	30.5
Diabetes mellitus type 2	2138	16.4	2186	20.4	4236	16.9	3834	19.7
Drugs history (in 6 months prior to index date)								
Antipsychotics	850	6.5	645	6.0	599	2.4	588	3.0
Antidepressants	3903	29.9	3075	28.6	4471	17.8	3681	18.9
Anticonvulsants	1015	7.8	589	5.5	992	4.0	722	3.7
Anti-Parkinson drugs	431	3.3	264	2.5	310	1.2	205	1.1
Corticosteroids (systemic and inhaled)	2950	22.6	2197	20.5	4564	18.2	3467	17.8
Benzodiazepines and other sedatives	2377	18.2	1954	18.2	2661	10.6	2567	13.2
Narcotic analgesics stronger than tramadol	1109	8.5	900	8.4	1023	4.1	989	5.1

Table 1 (continued)

	Patients with a hip fracture				Patients without a hip fracture			
	eGFR > 60 ml/min		CKD stages G3–G5		eGFR > 60 ml/min		CKD stages G3–G5	
Characteristic	*N* = 13,047	%	*N* = 10,733	%	*N* = 25,072	%	*N* = 19,511	%
Bisphosphonates	1690	13.0	1304	12.1	2511	10.0	2002	10.3
Anti-osteoporosis treatment[d]	1756	13.5	1349	12.6	2588	10.3	2068	10.6
Denosumab	3	0.0	4	0.00	11	0.0	4	0
HRT[e] and SERMs	101	0.8	42	0.4	260	1.0	117	0.6
Vitamin D (cholecalciferol and ergocalciferol)	2545	19.5	1933	18.0	3641	14.5	3225	16.5
Dihydrotachysterol	0	0	0	0	0	0	0	0
Alfacalcidol and calcitriol	17	0.1	164	1.5	25	0.1	212	1.1
Calcium	119	0.9	114	1.1	162	0.6	170	0.9
Loop diuretics	2502	19.2	3970	37.0	3803	15.2	6263	32.1
Thiazide diuretics	2234	17.1	2245	20.9	5997	23.9	5347	27.4
RAAS inhibitors	4631	35.5	5092	47.4	10,324	41.2	10,672	54.7
Insulin	1624	12.4	1675	15.6	3014	12.0	2699	13.8
Metformin	1134	8.7	869	8.1	2350	9.4	1586	8.1
Sulfonylurea	664	5.1	761	7.1	1186	4.7	1309	6.7
Thiazolidinedione	159	1.2	171	1.6	237	0.9	240	1.2
Dipeptyl peptidase-4 inhibitor	74	0.6	105	1.0	213	0.8	173	0.9
Other non-insulin anti-diabetic drugs	29	0.2	34	0.3	71	0.3	40	0.2

CKD chronic kidney disease, *IQR* interquartile range, *SD* standard deviation, *HRT* hormone replacement therapy, *SERM* selective oestrogen-receptor modulator, *RAAS* renin-angiotensin- aldosterone system

The "Kidney Disease: Improving Global Outcomes" (KDIGO) classification for CKD consists of five stages: G1: eGFR > 90 ml/min/1.73 m^2, G2: eGFR 60–89 ml/min/1.73 m^2, G3: eGFR 30–59 ml/min/1.73 m^2, G4: eGFR 15–29 ml/min/1.73 m^2 and G5: eGFR < 15 ml/min/1.73 m^2

[a] Fragility fracture: humerus, distal fore-arm and clinical vertebrae

[b] As defined by FRAX (anorexia nervosa, celiac disease, diabetes mellitus type 1, hypogonadism, osteogenesis imperfecta, osteomalacia, liver disease (cirrhosis, hepatitis and neoplasms), malnutrition, malabsorption and premature menopause)

[c] Crohn's disease and ulcerative colitis

[d] Bisphosphonates, strontium ranelate, calcitonin, PTH, denosumab

[e] Includes oestrogen treatment

Patients with no recorded eGFR in the year before the index date are not shown in this table. *N* = 14,040 for the hip fracture cohort and *N* = 29,857 for the control cohort

eGFR > 60 ml/min, the mean age was 79.2 years (SD = 9.7) and 69.8% was women. In the group of CKD stages G3–G5, the mean age was 84.2 years (SD = 7.5) and 76.3% was women. Mean BMI was higher in the CKD stages G3–G5 patients: 26.1 kg/m^2 in CKD stages G3–G5 vs. 25.3 kg/m^2 in eGFR > 60 ml/min. The median follow-up time (from hip fracture until the end of data collection) was 2.4 years (IQR 4.2) in eGFR > 60 ml/min and 1.8 years (IQR 3.8) in CKD stages G3–G5.

Incidence rates and risk of a subsequent major non-hip fragility fracture after initial hip fracture

The incidence rates (IRs) for a subsequent major non-hip fragility fracture after an initial hip fracture in the group of eGFR > 60 ml/min and CKD stages G3–G5 were 20.0 per 1000 person years and 19.1 per 1000 person years, respectively. The adjusted HR of subsequent major non-hip fragility fracture in the CKD stages G3–G5 group was not statistically significantly different from the eGFR > 60-ml/min group (adjusted HR 0.89; 95% confidence interval 0.79 to 1.00). Stratification for CKD stages showed for CKD stage G3 an adjusted HR of 0.89 (0.79 to 1.01), for CKD stage G4 0.88 (0.64 to 1.20) and for CKD stage G5 0.56 (0.20 to 1.56). Stratification by age did not show a significant difference in patients aged < 80 years compared to 80+ (Table 2).

Incidence rates and risk of any subsequent non-hip fracture after initial hip fracture

The IRs for any subsequent non-hip fracture after hip fracture were 52.1 per 1000 person years in eGFR > 60 ml/min and 48.1 per 1000 person years in CKD stages G3–G5 (Table 3).

Table 2 Kidney function and risk of subsequent major non-hip fragility fractures and risk of mortality after initial hip fracture

	Major non-hip fragility fractures after initial hip fracture				Mortality after initial hip fracture (in dataset with MOF as outcome)			
	Fractures $N = 1855$	Incidence rate/1000 py	Age/sex adj. analysis (HR; 95% CI)	Adj. analysis[a] (HR; 95% CI)	Deaths $N = 15{,}828$	Incidence rate/1000 py	Age/sex adj. analysis (cs-HR; 95% CI)	Adj. analysis[b] (cs-HR; 95% CI)
KDIGO CKD stage[c]								
eGFR > 60 ml/min	783	20.0	1.00 (reference)		5349	136.7	1.00 (reference)	
CKD G3-G5	486	19.1	0.90 (0.80–1.01)	0.89 (0.79–1.00)	5144	201.7	1.14 (1.10–1.19)	1.05 (1.01–1.09)
Stratified by sex[d]								
Men	66	12.5	0.98 (0.72–1.32)	0.96 (0.71–1.31)	1420	269.8	1.18 (1.10–1.26)	1.09 (1.02–1.18)
Women	420	20.7	0.89 (0.78–1.01)	0.88 (0.77–1.00)	3724	184.0	1.13 (1.08–1.19)	1.04 (0.99–1.09)
Stratified by age[e]								
< 80 years	123	20.0	0.98 (0.79–1.21)	0.91 (0.74–1.14)	723	117.8	1.32 (1.20–1.44)	1.09 (0.99–1.20)
≥ 80 years	363	18.7	0.87 (0.76–1.01)	0.88 (0.77–1.02)	4421	228.2	1.11 (1.07–1.16)	1.04 (1.00–1.09)
Kidney function stratified by CKD stage								
CKD G3	437	19.1	0.90 (0.80–1.01)	0.89 (0.79–1.01)	4200	183.6	1.04 (1.00–1.08)	0.98 (0.94–1.03)
CKD G4	45	19.4	0.93 (0.69–1.26)	0.88 (0.64–1.20)	773	332.8	1.80 (1.67–1.94)	1.50 (1.38–1.62)
CKD G5	< 5[f]	12.8	0.66 (0.25–1.77)	0.56 (0.20–1.56)	171	548.3	3.72 (3.20–4.32)	2.93 (2.48–3.46)
Stratified by history of dialysis								
Yes	< 5[f]	10.4	0.56 (0.08–3.96)	0.47 (0.06–3.41)	44	456.0	3.22 (2.40–4.32)	2.73 (2.00–3.72)
No	< 5[f]	13.9	0.71 (0.23–2.19)	0.60 (0.19–1.92)	127	589.7	3.93 (3.30–4.67)	3.00 (2.49–3.61)

HR hazard ratio, *CI* confidence interval, *CKD* chronic kidney disease, *py* person year, *Adj* adjusted, *MOF* major osteoporotic fracture

The following potential confounders were considered at baseline: sex, smoking status, alcohol use and body mass index. The adjustments for the use of drugs where for the 6-month period before the start of an interval. Other confounders were determined time-dependently at the start of each new interval

All analyses are adjusted for unknown eGFR status, but results of missing/unknown eGFR groups are not shown

[a] Adjusted for age, sex, body mass index, history of major osteoporotic fracture, diabetes mellitus type 2, use of active vitamin D, use of antidepressants and use of loop diuretics

[b] Adjusted for age, sex, body mass index, heart failure, ischaemic heart disease, hypertension, use of anti-psychotics, anti-osteoporotic drugs, active vitamin d, raas-inhibitors, loop diuretics, thiazides, insulin

[c] Sum of number of fractures and number of deaths do not add up, since missing eGFR is not shown (586 fractures with missing eGFR and 5335 deaths with missing eGFR)

[d] Compared to people with the same gender

[e] Compared to people within the same age group

[f] Exact number not shown due to privacy restrictions

Table 3 Kidney function and risk of any subsequent non-hip fractures and risk of mortality after initial hip fracture

	Risk of any subsequent non-hip fracture after hip fracture				Mortality after initial hip fracture (in dataset with any fracture as outcome)			
	Fractures $n = 4413$	Incidence rate/1000 py	Age/sex adj. analysis (HR; 95% CI)	Adj. analysis[a] (HR; 95% CI)	Deaths $n = 14{,}919$	Incidence rate/1000 py	Age/sex adj. analysis (cs-HR; 95% CI)	Adj. analysis[b] (cs-HR; 95% CI)
KDIGO CKD stage[c]								
eGFR > 60 ml/min	1892	52.1	1.00 Reference		5004	137.8	1.00 Reference	
CKD G3-G5	1153	48.1	0.89 (0.83–0.96)	0.90 (0.83–0.97)	4858	202.7	1.14 (1.09–1.19)	1.06 (1.01–1.10)
Stratified by sex[d]								
Men	185	36.9	1.05 (0.88–1.26)	1.05 (0.87–1.26)	1362	271.8	1.18 (1.10–1.27)	1.11 (1.03–1.19)
Women	968	51.1	0.86 (0.80–0.94)	0.87 (0.80–0.95)	3496	184.4	1.13 (1.08–1.18)	1.04 (0.99–1.10)
Stratified by age[e]								
< 80 years	273	47.0	0.94 (0.82–1.08)	0.94 (0.82–1.08)	691	119.1	1.31 (1.19–1.44)	1.09 (0.99–1.21)
≥ 80 years	880	48.4	0.87 (0.80–0.95)	0.88 (0.80–0.96)	4167	229.4	1.11 (1.06–1.16)	1.05 (1.00–1.10)
Kidney function stratified by CKD stage								
CKD G3	1031	47.9	0.89 (0.82–0.96)	0.90 (0.83–0.97)	3974	184.6	1.04 (1.00–1.08)	0.99 (0.94–1.03)
CKD G4	108	50.2	0.94 (0.77–1.14)	0.93 (0.76–1.13)	724	336.5	1.79 (1.66–1.94)	1.53 (1.42–1.66)
CKD G5	14	47.6	0.94 (0.55–1.59)	0.83 (0.48–1.44)	160	544.3	3.70 (3.16–4.33)	3.09 (2.60–3.67)
Stratified by history of dialysis								
Yes	6	63.8	1.31 (0.59–2.92)	1.11 (0.49–2.56)	43	457.3	3.24 (2.40–4.38)	3.00 (2.19–4.11)
No	8	40.0	0.77 (0.39–1.55)	0.70 (0.34–1.42)	117	585.2	3.90 (3.24–4.68)	3.13 (2.58–3.79)

HR hazard ratio, *CI* confidence interval, *CKD* chronic kidney disease, *py* person year, *Adj* adjusted, *MOF* major osteoporotic fracture

The following potential confounders were considered at baseline: sex, smoking status, alcohol use and body mass index. The adjustments for the use of drugs where for the 6-month period before the start of an interval. Other confounders were determined time-dependently at the start of each new interval

All analyses are adjusted for unknown eGFR status, but results of missing/unknown eGFR groups are not shown

[a] Adjusted for age, sex, body mass index, history of major osteoporotic fracture, diabetes mellitus type 2, use of active vitamin d, use of antidepressants and use of loop diuretics

[b] Adjusted for age, sex, body mass index, heart failure, ischaemic heart disease, hypertension, use of anti-psychotics, sedatives, anti-osteoporotic drugs, active vitamin d, loop diuretics, thiazides, raas-inhibitors, insulin

[c] Sum of number of fractures and number of deaths do not add up, since missing eGFR is not shown (1368 fractures with missing eGFR and 5057 deaths with missing eGFR)

[d] Compared to people with the same gender

[e] Compared to people within the same age group

Compared to eGFR > 60 ml/min, CKD stage G3 was associated with a lower risk of any subsequent non-hip fracture (adjusted HR 0.90 (0.83 to 0.97)). The risk of subsequent fractures in CKD stage G4 and G5 was not significantly different in comparison to eGFR > 60 ml/min. Stratification by sex demonstrated a lower risk in women, adjusted HR 0.87 (0.80 to 0.95).

Mortality

The IR for mortality after initial hip fracture was 136.7 per 1000 person years in eGFR > 60 ml/min and 201.7 for CKD stages G3–G5. In CKD stage G5, the IR was 548.3. The cs-HRs for mortality are shown in Table 2. Mortality risk was significantly higher in CKD stages G3–G5 compared to eGFR > 60 ml/min (cs-HR 1.05 (1.01 to 1.09)). Stratification by CKD stage resulted in a 1.5 higher mortality risk for CKD stage G4 (cs-HR 1.50 (1.38 to 1.62)) and a 3-fold higher mortality for CKD stage G5 (cs-HR 2.93 (2.48 to 3.46)) Fig. 1.

Figure 1 shows the cumulative incidence of the different outcomes (subsequent fracture and alive, subsequent fracture and death, death, alive and no subsequent fracture) for the different CKD stages.

Sensitivity analyses

In the non-hip fracture cohort (control cohort), the IRs of first major non-hip fragility fracture were 9.9 per 1000 person years in eGFR > 60 ml/min and 11.7 in CKD stages G3–G5 (Supplemental Table 1). The IRs in the non-hip fracture group were lower than in the study group after first hip fracture. The risk of major non-hip fragility fracture and the risk of any non-hip fracture in the non-hip fracture group did not differ significantly between CKD stages G3–G5 and eGFR > 60 ml/min (Tables 1 and 2, supplemental tables). Patients with CKD stage G3 had a lower risk of any non-hip fracture compared to eGFR > 60 ml/min (HR 0.93; 0.87 to 0.99). In the non-hip fracture group, also higher IRs of mortality in CKD stages G3–G5 were found. Mortality risk was significantly higher in CKD stages G3–G5 compared to eGFR > 60 ml/min (cs-HR 1.08 (1.05 to 1.12). Stratification by CKD stage resulted in an increased mortality risk in CKD stage G4 and CKD G5 (Supplemental Tables 1 and 2). In the control cohort, the cumulative incidence of the different outcomes (MOF and alive, MOF and death, death, alive and no MOF) in the CKD stages were calculated (Supplemental Fig. 2).

The sensitivity analyses in the high-risk subjects with a history of falling or a history of a fragility fracture showed similar results for the risk of subsequent major fragility fracture and mortality as in the hip fracture population. Further, CKD stages G3–G5 were not associated with subsequent fracture risk if the analysis was restricted to the first and the second year after index date. The mortality risk in the first year was higher in the CKD stages G3–G5 group compared to eGFR > 60 ml/min (cs-HR 1.16, 1.09 to 1.23). Stratification for CKD demonstrated an increasing mortality risk in CKD stages G3, G4 and G5. In the second year, the mortality risk was not increased in CKD stages G3–G5 compared to eGFR > 60 ml/min (cs-HR 0.99, 0.90 to 1.10). However, stratification for CKD showed an increased mortality risk in CKD

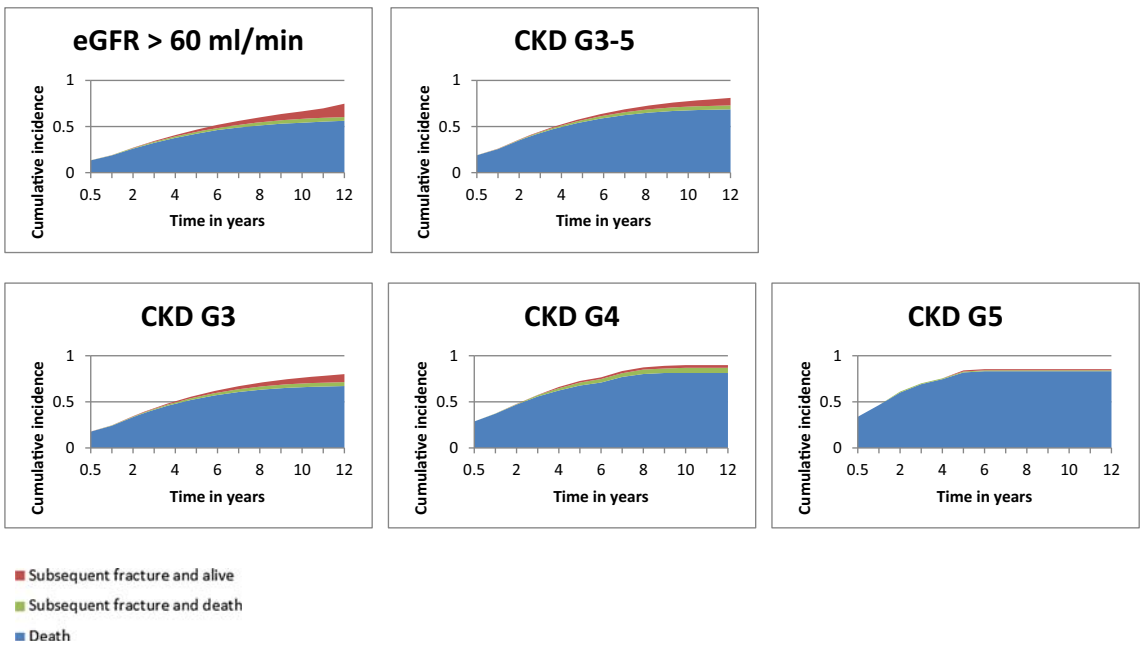

Fig. 1 Cumulative incidence of different outcomes after the initial hip fracture by kidney function. Subsequent fracture is a subsequent major osteoporotic fracture

stage G4 and CKD stage G5 (CKD stage G4 cs-HR 1.43, 1.16 to 1.76; CKD stage G5 cs-HR 2.81, 1.79 to 4.42) as compared to eGFR > 60 ml/min. In the non-hip fracture cohort, HRs for fracture and mortality in the first and second year were comparable with the hip fracture cohort.

Discussion

In this study, CKD stages G3–G5 were not associated with the risk of subsequent major non-hip fragility fractures following a hip fracture compared to eGFR > 60 ml/min. However, CKD stage G3–G5 were associated with a lower risk of subsequent any non-hip fracture and increased risk of all-cause mortality. Risk of all-cause mortality was 1.5- to 3-fold higher in patients with CKD G4 and G5 as compared to eGFR > 60 ml/min. In the non-hip fracture cohort, there was no increased risk of major non-hip fragility fractures in CKD G3–G5 compared to eGFR > 60 ml/min, but the mortality risk was increased in CKD G3–G5.

One of the strengths of this study is that it is a large, population-based cohort, which is representative for the UK population. While patients with CKD, especially stages G4–G5, have regular check-ups with nephrologists, it was demonstrated by Jameson et al. that the prevalence of CKD stages G3–G5 in 2010 in the CPRD was consistent with the prevalence found in other large cross-sectional studies and a national survey [21]. Furthermore, in this CPRD cohort, longitudinal data was available for risk factors allowing adjustment for several confounders including comorbidities, falling, risk factors for osteoporosis, use of drugs and lifestyle factors. Our study has several limitations. First, in this study, only community-dwelling patients were included. In 2014, Gibson-Smith et al. demonstrated in a hip fracture cohort from CPRD that 10% of the patients were transferred out of the database after hip fracture. A possible reason for this was that patients were transferred to nursing homes [22]. The mortality risk might be higher in the nursing home population than in the community-dwelling population. But this study provides no evidence on this population. Another limitation was that we were not able to study subsequent hip fracture due to the coding practices in UK primary care (it is difficult to differentiate between repeat recording of a previous fracture and new recording of an incident fracture). Further, our data source contains insufficient information to adequately identify CKD stages according to the KDOQI or KDIGO guidance with a CGA classification, based on cause, GFR category and albuminuria category. Since we did not have data on proteinuria and cause, we were not able to differentiate between CKD stage G1, stage G2 and no CKD in the eGFR category of > 60 ml/min.

This is the first study that evaluated subsequent fracture risk after hip fracture in patients with CKD. Previous studies focused on the association between CKD and the risk of a first fragility fracture. The studies of Nickolas et al., Dukas et al., Alem et al., Chen et al. and Dooley et al. showed an increased risk with worsening kidney function [2–6]. In contrast to these studies, we found no association of CKD with subsequent major non-hip fragility fracture risk after a hip fracture and the risk of any subsequent non-hip fracture was even lower in CKD stages G3–G5 compared to eGFR > 60 ml/min. This difference might be attributable to the higher mortality rate in CKD patients who sustained a hip fracture. Further, Nickolas et al. and Dukas et al. both performed a cross-sectional study [2, 3], whereas our study was a retrospective cohort study. The longer follow-up in three of the studies also might contribute to the different results [4–6]. Alem et al. performed the study in a dialysis population. The dialysis population has a higher fracture risk than CKD stages G3 and G4. We did exclude dialysis patients and that might explain the higher fracture risk in the study of Alem et al. [4]. However, one Canadian population-based cohort study of 1.8 million participants aged > 18 years did not find an association of increased fracture rates (hip, vertebrae and wrist) with an eGFR < 60 ml/min, independent of age and sex. The median follow-up was 4.4 years, median age was 47 years and 7.1% had an eGFR < 60 ml/min [23]. These results are in line with our result of no increased fracture risk in CKD G3–G5 compared to eGFR > 60 ml/min. The main differences of the studies are the median age, median follow-up and the outcome: fragility fractures in the Canadian cohort and subsequent fractures in our hip fracture cohort.

Our results of a 1.5- and 3-fold increased risk of mortality with CKD stages G4 and G5 after hip fracture are in line with the results of Nitsch et al. [24], although Nitsch et al. studied the hip fracture-related mortality instead of all-cause mortality post-hip fracture as we did in our analyses. Nitsch et al. showed in a population of 13,167 UK patients (median age of 80.3 years (IQR 77.2–84.1), 61% women, median follow-up 7.25 years (IQR 3.79–8.77)) a doubled risk of hip fracture-related mortality with an eGFR < 45 ml/min [24]. Our results are not fully in line with the results of Robertson et al. [25], who showed an increased post-hip fracture mortality risk (all-cause mortality post-hip fracture and hip fracture-related mortality post-hip fracture) for patients with CKD stage G4 but not for patients with CKD stages G3a, G3b, G5, G3–G5. However, in that study, patients aged 15 and older were included, and the mean age of the CKD stages G3–G5 population was lower than in our study (74.8 vs. 84 years) [25]. The lower mean age in the population of Robertson et al. might explain the differences in mortality risk. In our control patients, the mortality risk was increased in the same range as in the post-hip fracture patients in stages G3–G5, G4 and G5. CKD has been associated with an increased risk of mortality and cardiovascular mortality

which may explain our results of an increased mortality risk in both the hip fracture and control cohort [26, 27].

An unexpected finding in this study was that CKD after hip fracture was not associated with subsequent non-hip (fragility) fracture. A competing risk of all-cause mortality may be a sensible explanation for these observations. Over the past years, there has been more awareness of competing risks in research including elderly [28, 29]. Not accounting for competing risks may result in overestimated incidence rates and HRs. Competing risks are mainly relevant when the follow-up period is longer than 5 years, or when the competing event occurs equal or more often than the outcome of interest [30]. In the present study, 15,828 patients had died while only 1855 had suffered from a major non-hip fragility fracture after the index hip fracture. Surprisingly, we found no increased risk of a subsequent major non-hip fragility fracture with a worsening CKD stage. However, when we studied the cause-specific HR, we found an increased risk of mortality with a worsening CKD. We think that as a consequence of the high mortality rates in the group of patients with a worse kidney function, these patients were less susceptible to a new fracture. Due to the high mortality rates, the median exposure time was shorter, especially in the hip fracture cohort. This could then have resulted in the findings of the present study, showing no association between CKD stage and risk of subsequent fracture. We think that in the non-hip fracture group, the control cohort, the competing risk of fracture and death also might have resulted in the finding of no increased risk of major non-hip fragility fractures with worsening CKD stage. Presence of a competing risk of fracture and death in elderly with CKD has been reported previously [31, 32].

Our results showed that the major non-hip fragility fracture IR in our hip fracture cohort was higher as compared to the IR of major non-hip fragility fracture in the non-hip fracture cohort, which is in line with previous research that showed that a previous fracture increased the risk of a subsequent fracture [7–10]. However, the IRs for mortality were in both cohorts about 10 times higher than the IRs for major non-hip fragility fracture, showing that with respect to the absolute risks, mortality occurs much more frequently and is potentially of more clinical importance in this case.

In conclusion, this study did not demonstrate an increased risk of subsequent major non-hip fragility fractures following a hip fracture in patients with CKD stages G3–G5 compared to eGFR > 60 ml/min. In addition, there also was no association between major non-hip fragility fracture risk and renal function in the control population. However, mortality risk was substantially increased in both cohorts of hip fracture and non-hip fracture patients with CKD stages G4 and G5 as compared to eGFR > 60 ml/min. The elevated mortality risk may (up to > 500 per 1000 person years), as competing risk, explains our main finding that CKD stages G3–G5 should not be regarded as an important additional risk fracture for subsequent fractures in this population. Nevertheless, the absolute fracture risk in this population is still around 50 per 1000 person years. This emphasises the need of adequate management of renal failure especially since the options for anti-osteoporosis treatment in patients with eGFR < 30 ml/min are limited.

Compliance with ethical standards

Conflict of interest Dr. Wyers, Dr. Souverein, Dr. van Staa and Dr. Driessen have nothing to disclose.

Dr. de Bruin reports personal fees from Pfizer, personal fees from Novartis, personal fees from Sanofi, outside the submitted work; Dr. van den Bergh reports grants and personal fees from Amgen, grants and personal fees from Eli Lilly, personal fees from UCB, outside the submitted work; Dr. Geusens reports grants and personal fees from Amgen, grants from Pfizer, grants from MSD, grants from UCB, grants from Abbott, grants and personal fees from Lilly, grants from BMS, grants from Novartis, grants from Roche, grants from Will Pharma, outside the submitted work; Dr. de Vries supervises various PhD students who are employed with F. Hoffmann la Roche Ltd. (Welwyn Garden City UK and Basel, Switzerland). The topics of their PhDs are not related to the current work. Dr. de Vries has not received any fees or reimbursements for this.

Ethical considerations Ethical approval by the institutional or national research ethics committee was not required.

For this type of study, formal consent is not required.

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