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Kidney Function and Fracture Risk: The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background—People with end-stage renal disease are at high risk of bone fracture. Less is known about fracture risk in milder chronic kidney disease (CKD), and whether CKD-associated fracture risk varies by sex or assessment with alternative kidney markers.

Study Design—Prospective cohort study.

Setting & Participants—10,955 participants from the Atherosclerosis Risk in Communities (ARIC) Study followed up from 1996 to 2011.

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Contributions: Research idea and study design: ES, MEG; data acquisition: ND, ALCS, JC, MEG; data interpretation: ND, AV, ALCS, SB, MMD, JC, LJA, ES, MEG; statistical analysis: ND, AV, MEG; critical revisions to manuscript: ND, AV, ALCS, SB, MMD, JC, LJA, ES, MEG. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. MEG takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Table S1: Baseline characteristics of study participants with available CMS data, by eGFR_{Cr} and albuminuria status.

Figure S1: Adjusted HR of fracture-related hospitalization according to baseline albuminuria and eGFR_{Cr}, by age

Note: The supplementary material accompanying this article (doi: _____) is available at www.ajkd.org

Supplementary Material Descriptive Text for Online Delivery

Supplementary Table S1 (PDF). Baseline characteristics of study participants with available CMS data, by eGFR_{Cr} and albuminuria status.

Supplementary Figure S1 (PDF). Adjusted HR of fracture-related hospitalization according to baseline albuminuria and eGFR_{Cr}, by age.

Predictor—Kidney function as assessed by creatinine-based estimated glomerular filtration rate (eGFR_{Cr}), urine albumin-creatinine ratio (ACR), and alternative filtration markers.

Outcomes—Fracture-related hospitalizations determined by diagnostic code.

Measurements—Baseline kidney markers; hospitalizations identified by self-report during annual telephone contact and active surveillance of local hospital discharge lists.

Results—Mean age of participants was 63 years, 56% were female, and 22% were black. During a median follow-up of 13 years, there were 722 incident fracture-related hospitalizations. Older age, female sex, and white race were associated with higher risk of fracture ($p < 0.001$). The relationship between eGFR_{Cr} and fracture risk was non-linear: below 60 ml/min/1.73 m², lower eGFR_{Cr} was associated with higher fracture risk (adjusted HR per 10 ml/min/1.73 m² lower, 1.24; 95% CI, 1.05–1.47); there was no statistically significant association above 60 ml/min/1.73 m² in the primary analysis. In contrast, there was a graded association between other markers of kidney function and subsequent fracture, including ACR (HR per doubling, 1.10; 95% CI, 1.06–1.14), cystatin C–based eGFR (HR per 1-SD decrease, 1.15; 95% CI, 1.06–1.25), and 1/β₂-microglobulin (HR per 1-SD decrease, 1.26, 95% CI, 1.15–1.37).

Limitations—No bone mineral density assessment; one-time measure of kidney function.

Conclusions—Both low eGFR and higher albuminuria were significant risk factors for fracture in this community-based population. The shape of the association in the upper ranges of eGFR varied by the filtration marker used in estimation.

Keywords

bone fracture; fracture risk; kidney filtration markers; chronic kidney disease (CKD); estimated glomerular filtration rate (eGFR); albuminuria; albumin-creatinine ratio (ACR); renal function; hospitalization; hospitalized fracture

Kidney disease has profound effects on bone. Alterations in mineral metabolism and bone architecture in the setting of reduced estimated glomerular filtration rate (eGFR) are well established, and observational studies suggest that hemodialysis patients have 25.6 fractures per 1000 patient-years, a rate far greater than in the general population [1]. However, the literature examining fracture risk in persons with earlier stages of chronic kidney disease (CKD) – and particularly the independent associations with eGFR and albuminuria – is limited. Furthermore, there is some suggestion that kidney function is associated with fractures in women but not in men [2, 3].

Recent guidelines suggest classifying CKD by both level of eGFR and level of albuminuria [4]. Albuminuria and eGFR are only loosely correlated and display different risk associations with adverse outcomes [5]. For example, log-transformed albuminuria is associated with mortality risk in a linear manner, whereas eGFR based on serum creatinine (eGFR_{Cr}) displays higher mortality risk at both lower and higher levels of eGFR_{Cr} [6]. The U-shaped association with mortality may reflect the fact that eGFR_{Cr} is influenced by not only kidney function but also muscle mass, which may be an important determinant in fracture risk [6]. Kidney function estimated by other filtration markers may be superior to eGFR_{Cr} in predicting fracture risk [3, 7]. For example, frail individuals are more likely to

have falls and fracture, and the kidney filtration marker cystatin C (eGFR_{Cys}) may be more strongly correlated with frailty than eGFR_{Cr} [8, 9]. Whether eGFR_{Cys} and other markers of kidney filtration are associated with fracture risk independent of eGFR_{Cr} is unknown.

In the present study, we examined the association between kidney function and hospitalized fracture in the Atherosclerosis and Risk in Communities (ARIC) Study, a community-based cohort of mostly black and white adults, aged 52–75 years at baseline. We compared the risk of hospitalized fracture in persons with and without CKD, evaluating the graded association between eGFR_{Cr}, albuminuria, and fracture risk. Additionally, we examined the same associations using alternative markers of filtration function, including eGFR_{Cys}, β_2 -microglobulin (B2M), and β -trace protein (BTP). Finally, given that previous studies demonstrated differences in associations between kidney function and fracture rates between men and women, we formally tested for interaction between sex and kidney function markers with fracture risk.

METHODS

Study Population

Participants of the ARIC study were recruited from four communities in the United States: Forsyth County, North Carolina; Washington County, Maryland; suburbs of Minneapolis, Minnesota; and Jackson, Mississippi. During the initial examination (visit 1), participants were aged 45–64 years of age. Visit 1 took place in 1987–1989; visit 2, 1990–1992; visit 3, 1993–1995; visit 4, 1996–1998; and visit 5, 2011–2013. For the purposes of the present study, visit 4 (N= 11,440) was used as the “baseline” visit since this was the first visit in which urine albumin-creatinine ratio (ACR) was measured. We excluded participants with a fracture prior to visit 4 (n=245). We also excluded persons with missing data on key covariates: BMI (n=20), diabetes (n=50), smoking status (n=18) and prevalent coronary heart disease (n=84). In addition, we excluded participants who were not white or black (n=30) as well as all blacks from Minneapolis (n=12) and Washington County (n=26). Thus, 10,955 participants were included in the final study population.

Ascertainment of Hospitalized Bone Fracture

Hospitalized bone fracture events were defined as the following International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), codes from hospitalization discharges: 733.1–733.19, 733.93–733.98, or 800–829.

Hospitalizations were identified through two primary sources: patient self-report during annual telephone contact and active surveillance of hospital discharges in the communities in which the participants were recruited. For each identified hospitalization, up to 26 discharge diagnostic codes were abstracted. Relevant fracture ICD-9-CM codes could be present in any diagnostic code position (e.g., primary or secondary diagnosis).

Ascertainment of Kidney Function

Kidney function at visit 4 was classified in multiple ways. In the primary analysis, kidney function was assessed as eGFR_{Cr} (calculated using the CKD-EPI [CKD epidemiology

Collaboration] 2009 equation [10] from plasma creatinine calibrated to an IDMS-traceable reference method) and albuminuria ($\log_2$ -transformed urine ACR (in mg/g)). Plasma and urine creatinine were measured by the modified kinetic Jaffe method. Albumin was measured from urine samples by a nephelometric method either on the Dade Behring BN100 or on the Beckman Image Nephelometer. Because the relationship between eGFR_{Cr} and fracture appeared non-linear in locally-weighted smoothing plots, eGFR_{Cr} was represented using linear splines with a knot at $60 \text{ ml/min/1.73 m}^2$. In separate analysis, kidney function was also categorized by eGFR_{Cr} and albuminuria stage according to the KDIGO (Kidney Disease: Improving Global Outcomes) guidelines: G1–G5 and A1–A3 [4]. Finally, kidney function was estimated using eGFR_{Cys} (using serum cystatin C calibrated and standardized to International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference [11] and converted to eGFR using the 2012 CKD-EPI cystatin C equation [12]) as well as the reciprocal of B2M and the reciprocal of BTP. B2M and BTP were measured from plasma samples using nephelometric technology run on the Dade Behring Nephelometer II (BNII) system.

Covariates

All covariates reflect baseline values at ARIC study visit 4. Body mass index (BMI) was defined as weight (in kg) divided by height (in m) squared and was analyzed using linear splines with a knot at 30 kg/m^2 . Age was analyzed continuously. Race was classified as black or white. Diabetes was defined as self-reported history of physician diagnosis, anti-diabetes medication use during the past two weeks, fasting blood glucose level $\geq 126 \text{ mg/dL}$ or non-fasting blood glucose level $\geq 200 \text{ mg/dL}$. Prevalent coronary heart disease was established via self-report at visit 1 or an adjudicated event between visits 1 and 4.

Cigarette smoking and alcohol consumption were categorized as current user or never/former user. Hypertension was defined by systolic blood pressure $\geq 140 \text{ mmHg}$, diastolic blood pressure $\geq 90 \text{ mm Hg}$ or self-reported hypertension medication use during the past two weeks. Menopausal status was classified as post-menopausal or premenopausal. Hormone use was defined as current/former estrogen and/or progestin user or never user.

Antidepressant, thiazide diuretic, loop diuretic, thiazolidinedione, bisphosphonate, proton pump inhibitor and glucocorticoid use was self-reported by participants and confirmed by staff from the medications brought to the visit.

Statistical Analysis

Baseline (1996–1998) characteristics were compared by eGFR_{Cr} and albuminuria categories using a test for linear trend to examine differences of continuous and categorical variables. Incidence rates and adjusted incident rate ratios by eGFR_{Cr} and albuminuria stages were determined by Poisson regression, and Cox proportional hazards regression was used to assess associations between risk factors and subsequent fracture. The demographically adjusted model (Model 1) adjusted for age, gender, and race and center. The fully adjusted model (Model 2) adjusted for variables in Model 1 as well as BMI, prevalent coronary heart disease, diabetes status, bisphosphonate use, proton pump inhibitor use, glucocorticoid use, cigarette smoking, and albuminuria levels. We tested for an interaction of eGFR_{Cr} /

albuminuria and sex with fracture risk by adding a product term between each marker of kidney function and sex to the covariates. We considered other adjustments: hypertension (including a separate binary variable indicating hypertension medication use), postmenopausal status (in women), alcohol use, use of hormone replacement therapy (in women), and specific medication use (e.g., thiazide diuretics, antidepressants). These factors were not included in the final model because they were not statistically significantly associated with fracture risk (all p -values > 0.05) and did not change inference for the other variables. Thiazolidinedione, a medication that has previously been associated with fracture, was not included in the analyses because few patients (0.5%) were taking the drug at baseline.

All analyses were repeated using novel kidney filtration markers to estimate kidney function, with and without adjustment for $eGFR_{Cr}$. We tested for non-linearity in the relationship between alternative kidney markers and the risk of fracture using linear splines, but the changes in slopes were not significant. Therefore, we modeled the novel kidney markers as linear terms. We also evaluated the risk of fracture in groups based on CKD classification according to $eGFR_{Cr}$ and $eGFR_{Cys}$, comparing persons with $eGFR_{Cr} < 60$ ml/min/1.73 m² and $eGFR_{Cys} < 60$ ml/min/1.73 m², $eGFR_{Cr} < 60$ ml/min/1.73 m² and $eGFR_{Cys} \geq 60$ ml/min/1.73 m², and $eGFR_{Cr} \geq 60$ ml/min/1.73 m² and $eGFR_{Cys} < 60$ ml/min/1.73 m² to those with $eGFR \geq 60$ ml/min/1.73 m² by both measures.

Finally, in sensitivity analysis, we also included non-hospitalized fractures as obtained through linkage with Centers for Medicare & Medicaid Services data. Fracture-related health encounters were identified during periods in which participants were enrolled in Medicare. These data were available beginning in 1999; 9,164 out of the 10,955 participants had at least one period of coverage. Baseline characteristics for the 9,164 participants are shown in Table S1 (provided as online supplementary material).

All P -values were two-sided, and $p < 0.05$ was considered statistically significant. Statistical analyses were conducted using Stata version 13 (StataCorp LP, College Station, TX).

RESULTS

Of the 10,955 persons included in the study population, 5,160 (47.10%) had $eGFR_{Cr}$ levels ≥ 90 ml/min/1.73 m² at baseline, 5,102 (46.57%) had $eGFR_{Cr}$ levels of 60–89 ml/min/1.73 m², and 693 (6.33%) had $eGFR_{Cr} < 60$ ml/min/1.73 m² (Table 1). The majority (91.76%) had normal to mildly increased ACR levels (< 30 mg/g) at baseline, 710 (6.48%) had moderately increased ACR levels (30–300 mg/g) and 193 (1.76%) had severely increased ACR levels (> 300 mg/g). Persons with lower $eGFR_{Cr}$ or higher ACR tended to be older and were more likely to be black, hypertensive, diabetic, and to have prevalent coronary heart disease than those with higher $eGFR_{Cr}$ or lower ACR. They were also more likely to have diabetic retinopathy (tested at ARIC visit 3). The population with lower $eGFR_{Cr}$ or higher ACR also had higher proportions of individuals taking antihypertensive medication, antidepressants, glucocorticoids and loop diuretics, and lower proportions of smoking, obesity, alcohol use, and estrogen/progestin hormone use (in women).

There were 722 incident cases of hospitalized fracture during a median of 13 years of follow-up. Site of fracture included skull (n=28); spinal column (n=77); ribs, sternum, larynx or trachea (n=48); pelvis (n=39); clavicle or scapula (n=6); arm (n=75); wrist (n=4); hand or finger (n=12); leg (n=246); ankle (n=77); foot (n=11); and unspecified (n=99). In the 13 years of follow-up, 2,131 persons died without having a fracture (1,846 with eGFR_{Cr} <60 ml/min/1.73 m²; 285 with eGFR ≥ 60 ml/min/1.73 m²). The relevant fracture ICD-9-CM code was the primary diagnostic code for 537 of the 722 incident cases.

The unadjusted rate of fracture was 5.53 (95% confidence interval [CI], 5.14–5.95) per 1,000 person-years of follow-up, with higher rates among those with lower eGFR_{Cr} or higher ACR levels. For example, the incident rates of fracture were 9.13 (95% CI, 7.16–11.64), 5.86 (95% CI, 5.28–6.50), and 4.81 (95% CI, 4.29–5.38) per 1,000 person-years among those with eGFR_{Cr} <60, 60–89, and ≥ 90 ml/min/1.73 m², respectively. By level of ACR, the incident rates of fracture were 5.25 (95% CI, 4.86–5.68), 8.50 (95% CI, 6.64–10.88), and 12.55 (95% CI, 8.18–19.24) per 1,000 person-years among those with ACR <30, 30–300, and >300 mg/g, respectively.

In analysis stratified by both stage of eGFR_{Cr} and albuminuria, the unadjusted incidence rates of fracture increased from 4.7 (95% CI, 4.2–5.3) to 24.6 (95% CI, 10.2–59.0) per 1,000 person-years with higher albuminuria and GFR stages (Figure 1A). The adjusted incidence rate ratios of fracture generally increased as well, from 1.0 (95% CI, 0.3–3.0) to 5.8 (95% CI, 2.4–14.2; reference group: eGFR ≥ 90 ml/min/1.73 m² and albuminuria <30 mg/g) with increasing albuminuria and GFR stages (Figure 1B).

In continuous analysis, there was a graded association between eGFR_{Cr} and fracture risk among those persons with eGFR_{Cr} levels below 60 ml/min/1.73 m². In this range, lower eGFR_{Cr} was associated with increased risk of fracture (adjusted hazard ratio [HR] per 10 ml/min/1.73 m² lower, 1.24; 95% CI, 1.05–1.47) (Table 2). There was a non-significant association between higher eGFR and fracture risk at eGFR_{Cr} ≥ 60 ml/min/1.73 m² (Figure 2a). Albuminuria was independently associated with fracture hospitalization (HR per two-fold increase, 1.10; 95% CI, 1.06–1.14) (Figure 2b). Other independent risk factors for fracture hospitalization included older age (HR per 10-years older, 2.25; 95% CI, 1.94–2.60), female sex (HR, 1.46; 95% CI, 1.25–1.72), current smoking (HR, 1.43; 95% CI, 1.17–1.76), diabetes (HR, 1.25; 95% CI, 1.02–1.54), glucocorticoid use (HR, 2.10; 95% CI, 1.45–3.04), bisphosphonate use (HR, 2.44; 95% CI, 1.53–3.90), and proton pump inhibitor use (HR, 1.43; 95% CI, 1.00–2.03). These associations were similar in analyses stratified by gender (Figure 3) and age (Figure S1). The relationship of eGFR_{Cr} and albuminuria with fracture was not significantly different between men and women (eGFR_{Cr} <60 mL/min/1.73 m²: p for interaction= 0.2; eGFR_{Cr} ≥ 60 ml/min/1.73 m²: p for interaction= 0.4; albuminuria: p for interaction= 0.6).

There was a linear relationship between lower eGFR and higher fracture risk when estimated with alternative filtration markers (Table 3). For example, a 1-standard deviation decrease in eGFR_{Cys} was associated with 1.15 (95% CI, 1.06–1.25) times increased risk of fracture in adjusted analyses. The relationship between the reciprocal of B2M and fracture demonstrated the strongest association (HR, 1.26, 95% CI, 1.15–1.37). Each filtration

marker remained significantly associated with fracture risk when $eGFR_{Cr}$ was included in the model.

Compared to persons with $eGFR \geq 60$ ml/min/1.73 m² by both creatinine and cystatin C, persons with $eGFR < 60$ ml/min/1.73 m² by both cystatin C and creatinine as well as by cystatin C only were at higher risk of fracture (adjusted HR for CKD by both markers, 1.45 [95% CI, 1.05–2.00]; aHR for CKD by cystatin C only, 1.53 [95% CI, 1.19–1.97]). Persons with $eGFR < 60$ ml/min/1.73 m² by creatinine but not cystatin C were not at higher risk of fracture (adjusted HR, 0.89, 95% CI, 0.56–1.41) (Table 4).

In sensitivity analyses incorporating 1,078 outpatient fracture events from CMS data in addition to fracture hospitalizations, associations between fracture and $eGFR_{Cr}$ were even stronger (< 60 ml/min/1.73 m²: adjusted HR per 10 ml/min/1.73 m² lower, 1.25 [95% CI, 1.06–1.48; $p=0.008$]; 60 ml/min/1.73 m²: adjusted HR per 10 ml/min/1.73 m² lower, 0.95 [95% CI, 0.90–1.00; $p=0.06$]). The relationship between albuminuria and fracture was similar, if slightly attenuated (adjusted HR per two-fold increase, 1.08; 95% CI, 1.04–1.12; $p<0.001$).

DISCUSSION

In this large prospective cohort study of middle-aged and older men and women, lower $eGFR_{Cr}$ level below the threshold of 60 ml/min/1.73 m² was associated with a higher risk of fracture during a median follow-up of 13 years. After adjustment for factors related to osteoporosis and reduced kidney function, this association was attenuated but still statistically significant. Additionally, higher albuminuria was independently associated with higher risk of fracture. Alternative filtration markers had stronger and more linear associations with hospitalized fractures than did $eGFR$ based on serum creatinine. These results suggest that CKD is a robust risk factor for hospitalized fracture, but that the non- $eGFR$ determinants of serum creatinine (e.g., muscle mass, protein intake) may lessen its utility in fracture risk prediction. Persons with low muscle mass, for example, will have falsely low creatinine and thus falsely high $eGFR_{Cr}$. This may confound the relationship between kidney function as assessed by serum creatinine and fracture risk.

The results of this study expand upon the current literature of fracture risk and CKD. Our finding of a graded association between albuminuria and fracture risk is generally consistent with that of Barzilay et al. [3], where a doubling of albuminuria, after adjustment for osteoporosis-related factors, $eGFR_{Cys}$, frailty, and falling, was associated with an increased risk of hip fracture. In their study of 3,110 older adults with up to 9.5 years of follow-up, the albuminuria-fracture association was present in older women but not in men. It is important to note that this study examined hip fractures only. Another study by the same author group [13] found an association between albuminuria and fracture only in those with macroalbuminuria but not microalbuminuria. In contrast, in the present study, albuminuria was an independent risk factor for any fracture-related hospitalization, irrespective of sex, and a dose-dependent relationship was observed. Naylor et al [14] found that the 3-year cumulative incidence of fracture in white Canadian men and women increased in a graded manner with a lower $eGFR_{Cr}$, independent of age. Our study expands on this finding by

including blacks in the study population and by rigorously evaluating the additional importance of ACR.

Not all studies have found an association between eGFR and increased risk of fracture. In a community based study of approximately 1.8 million adults, Elliot et al [16] found that persons with $\text{eGFR}_{\text{Cr}} < 60 \text{ ml/min/1.73 m}^2$ were not at increased rates of incident fractures (hip, wrist and vertebral) compared to persons with higher eGFR_{Cr} . However, there did appear to be a U-shaped relationship in hip fracture risk in certain age groups. In this study, however, laboratory measures were obtained from administrative records and thus the authors did not adjust for proteinuria, which is not uniformly measured in clinical practice.

An interesting finding in the present study was the stronger association of fracture risk and alternative filtration markers compared with eGFR_{Cr} . Creatinine is a biomarker known to be affected by muscle mass, such that frail individuals with low muscle mass may have an inappropriately high eGFR_{Cr} [17]. Cystatin C, B2M, and BTP have other non-GFR determinants (i.e. high C-reactive protein levels, low high-density lipoprotein cholesterol), but none may be as important as muscle mass in relation to fracture risk [18]. These results are partially consistent with those of Ensrud et al. [7] who found that older men with lower eGFR_{Cys} had an increased risk of hip fracture whereas lower eGFR_{Cr} or lower eGFR based on both creatinine and cystatin C was not associated with a higher age-adjusted hip fracture risk.

The relationship between CKD function and elevated fracture risk has clear biological plausibility. Bone and mineral abnormalities have long been recognized in persons with reduced eGFR. Recently, higher albuminuria has also been associated with increases in PTH, independent of eGFR [19]. Although PTH has anabolic as well as catabolic effects on the bone, the catabolic effects appear to be dominant in states of persistent PTH elevation [20]. For example, patients with primary hyperparathyroidism have a significantly higher risk of fracture than the general public [21]. In hemodialysis patients, higher levels of intact PTH have also been associated with higher rates of fracture [22]. Alternatively, the association between kidney disease and fracture might be driven by the development of frailty and sarcopenia, conditions related both to fracture risk and CKD [23].

This study has certain strengths and limitations that should be considered in the interpretation of the results. A community-based cohort of predominantly black and white individuals, the ARIC study is useful in evaluating the association of kidney function and fracture risk in a bi-ethnic population. We carefully accounted for multiple measures of kidney function, which were measured in a research setting. Although we relied on identification of fracture by hospitalization ICD-9-CM codes, a technique that may have lower sensitivity, this method likely identifies the cases of fracture which are most clinically important (high specificity). Results of sensitivity analyses incorporating outpatient fractures were similar. Because of the 15-year gap between study visits 4 and 5, we used a single measure of eGFR and ACR; kidney function at baseline may not represent kidney function at the time of fracture. Finally, we had no assessment of bone mineral density, as ARIC participants did not undergo routine dual energy X-ray absorptiometry scanning.

In summary, we found that lower eGFR_{Cr} and higher albuminuria were independently associated with risk of fracture, with similar effect sizes in both men and women. While eGFR_{Cr} was an independent risk factor for fracture risk at levels below 60 ml/min/1.73 m², alternative filtration markers demonstrated stronger and more linear associations with hospitalized fractures. Persons reclassified as having CKD on the basis of albuminuria or alternative filtration markers may be at a significant risk of fracture, suggesting the utility of a multi-marker approach to CKD identification.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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				Persistent albuminuria categories (mg/g) Description and range		
				A1 Normal to mildly increased	A2 Moderately increased	A3 Severely increased
				<30	30-300	>300
GFR categories (ml/min/1.73 m ²) Description and range	G1	Normal or high	≥90	4.7 (4.2, 5.3) (n=276/4,805)	6.7 (4.4, 10.2) (n=22/300)	5.6 (1.8, 17.4) (n=3/55)
	G2	Mildly decreased	60-89	5.7 (5.1, 6.3) (n=323/4,740)	8.1 (5.5, 11.9) (n=26/300)	12.5 (6.0, 26.2) (n=7/62)
	G3a	Mildly to moderately decreased	45-59	6.8 (4.8, 9.5) (n=33/438)	14.0 (7.5, 26.1) (n=10/76)	10.5 (2.6, 41.8) (n=2/21)
	G3b	Moderately to severely decreased	30-44	8.8 (4.0, 19.6) (n=6/64)	22.5 (8.4, 59.9) (n=4/28)	21.8 (8.2, 58.1) (n=4/25)
	G4/G5	Severely decreased/ Kidney failure	≤29	NA (n=0/5)	28.6 (4.0, 202.9) (n=1/6)	24.6 (10.2, 59.0) (n=5/30)
				Persistent albuminuria categories (mg/g) Description and range		
				A1 Normal to mildly increased	A2 Moderately increased	A3 Severely increased
				<30	30-300	>300
GFR categories (ml/min/1.73 m ²) Description and range	G1	Normal or high	≥90	1.0 (Reference)	1.3 (0.8, 2.0)	1.0 (0.3, 3.0)
	G2	Mildly decreased	60-89	1.2* (1.0, 1.4)	1.7** (1.1, 2.6)	3.0** (1.4, 6.5)
	G3a	Mildly to moderately decreased	45-59	1.5* (1.0, 2.2)	3.2*** (1.7, 6.0)	2.1 (0.5, 8.5)
	G3b	Moderately to severely decreased	30-44	1.8 (0.8, 4.1)	4.7** (1.7, 12.8)	4.2** (1.5, 11.4)
	G4/G5	Severely decreased/ Kidney failure	≤29	NA	4.8 (0.7, 34.5)	5.8*** (2.4, 14.2)

Figure 1.

A. Unadjusted incidence rates (per 1,000 person years) of fracture-related hospitalization by eGFR_{Cr} and albuminuria category at baseline (1996–1998).

* n=number of fractures/number of participants. Colors reflect ranking of risk of fracture-related hospitalization. Green: low risk; Yellow: moderately increased risk; Orange: high risk; Red: very high risk.

B. Adjusted incidence rate ratios[†] of fracture-related hospitalization by eGFR_{Cr} and albuminuria category at baseline (1996–1998).

* Colors reflect ranking of risk of fracture-related hospitalization. Green: low risk; Yellow: moderately increased risk; Orange: high risk; Red: very high risk. [†]Adjusted for age, gender, race-center, BMI, diabetes status, cigarette smoking, prevalent coronary heart disease, bisphosphonate use, proton pump inhibitor use and glucocorticoid use. *p 0.05, ** p 0.01, *** p 0.001

Figure 2.

Adjusted hazard ratio* (95% confidence interval) of fracture-related hospitalization by level of eGFR_{Cr} (A) and albuminuria (B) at baseline (1996–1998), with histogram of eGFR_{Cr} and albuminuria values.

*The solid lines in A and B are the predicted values from the Cox proportional hazards model; the dashed lines represent the corresponding 95% confidence intervals. eGFR_{Cr} is represented using linear splines (A), with a knot at 60 ml/min/1.73 m².

Figure 3. Adjusted hazard ratio* (95% confidence interval) of fracture-related hospitalization by level of eGFR_{Cr} and albuminuria at baseline (1996–1998), by sex.
*The solid lines are the predicted values from the Cox proportional hazards model; the corresponding 95% confidence intervals are included. eGFR_{Cr} is represented using linear splines, with a knot at 60 ml/min/1.73 m².

Table 1

Baseline characteristics of participants by eGFR_{cr} and albuminuria status at baseline, 1996–1998.

Variable	eGFR _{cr} (ml/min/1.73 m ²)				ACR, mg/g			p for trend
	<60 (n=693)	60–89 (n=5,102)	90 (n=5,160)	p for trend	<30 (n=10,052)	30–300 (n=710)	>300 (n=193)	p for trend
Age, y	67.2 (5.2)	65.0 (5.5)	61.0 (4.9)	<0.001	63.1 (5.6)	64.7 (5.7)	64.9 (6.1)	<0.001
Male sex	319 (46.0)	2,462 (48.3)	2,040 (39.5)	<0.001	4,391 (43.7)	333 (46.9)	97 (50.3)	0.02
Black race	161 (23.2)	859 (16.8)	1,350 (26.2)	<0.001	2,042 (20.3)	243 (34.2)	85 (44.0)	<0.001
BMI, kg/m ²	29.3 (5.4)	28.6 (5.1)	29.0 (6.0)	0.2	28.7 (5.5)	29.6 (6.3)	30.7 (6.3)	<0.001
Waist-to-hip ratio	0.97 (0.07)	0.95 (0.07)	0.94 (0.07)	<0.001	0.95 (0.07)	0.96 (0.07)	0.98 (0.07)	<0.001
Current smoker	73 (10.6)	577 (11.3)	969 (18.8)	<0.001	1,427 (14.2)	158 (22.3)	34 (17.6)	<0.001
Current drinker	270 (39.0)	2,567 (50.3)	2,590 (50.2)	0.001	5,082 (50.6)	293 (41.3)	52 (26.9)	<0.001
Diabetes [†]	188 (27.1)	734 (14.4)	882 (17.1)	0.08	1,408 (14.0)	275 (38.7)	121 (62.7)	<0.001
Hypertension [*]	494 (71.6)	2,426 (47.7)	2,237 (43.5)	<0.001	4,460 (44.5)	523 (73.8)	174 (90.6)	<0.001
Hypertension Medication use	507 (73.2)	2,263 (44.4)	1,978 (38.3)	<0.001	4,099 (40.8)	477 (67.2)	172 (89.1)	<0.001
Prevalent CHD	133 (19.2)	447 (8.8)	355 (6.9)	<0.001	766 (7.6)	118 (16.6)	51 (26.4)	<0.001
Medication use								
Glucocorticoids	27 (3.9)	103 (2.0)	93 (1.8)	0.006	193 (1.9)	17 (2.4)	13 (6.7)	<0.001
Antidepressants	64 (9.2)	326 (6.4)	323 (6.3)	0.04	630 (6.3)	63 (8.9)	20 (10.4)	0.001
Thiazide diuretics	89 (12.8)	408 (8.0)	355 (6.9)	<0.001	740 (7.4)	90 (12.7)	22 (11.4)	<0.001
Bisphosphonate	7 (1.0)	48 (0.9)	33 (0.6)	0.08	82 (0.8)	5 (0.7)	1 (0.5)	0.6
Loop diuretic	98 (14.1)	227 (4.5)	154 (3.0)	<0.001	364 (3.6)	68 (9.6)	47 (24.4)	<0.001
Benzodiazepines	61 (8.8)	330 (6.5)	267 (5.2)	<0.001	601 (6.0)	47 (6.6)	10 (5.2)	0.9
PPI	39 (5.6)	164 (3.2)	156 (3.0)	0.009	327 (3.3)	23 (3.2)	9 (4.7)	0.4
Prevalent Retinopathy ^{***}	46 (8.6)	147 (3.5)	144 (3.3)	<0.001	233 (2.8)	68 (12.1)	36 (25.7)	<0.001

Variable	eGFR _{cr} (mL/min/1.73 m ²)				ACR, mg/g		
	<60 (n=693)	60–89 (n=5,102)	90 (n=5,160)	p for trend	<30 (n=10,052)	30–300 (n=710)	>300 (n=193)
Postmenopausal **	351 (97.0)	2,377 (94.5)	2,588 (91.2)	<0.001	4,900 (93.0)	327 (92.9)	89 (96.7)
Hormone use **	82 (33.5)	728 (41.4)	1,020 (49.1)	<0.001	1,725 (45.8)	89 (35.2)	16 (26.7)
ACR, mg/g	5.9 [2.1–37.6]	3.5 [1.7–7.3]	3.8 [1.8–7.7]	<0.001	3.3 [1.6–6.3]	61.9 [41.7–121.6]	704.7 [429.4–1216.7]
>30 mg/g	186 (26.8)	361 (7.1)	351 (6.8)	<0.001	-	-	-
eGFR _{cr} , mL/min/1.73 m ²	49.7 ±10.7	78.1 ±8.1	99.1 ±7.6	<0.001	86.8 ±15.0	82.8 ±21.0	66.4 ±30.9
<60 mL/min/1.73 m ²	-	-	-	-	507 (5.0)	110 (15.5)	76 (39.4)
eGFR _{Cys} , mL/min/1.73 m ²	54.3 ±18.9	78.9 ±15.5	91.5 ±15.1	<0.001	84.2 ±17.4	76.2 ±21.5	58.4 ±28
<60 mL/min/1.73 m ²	415 (61.0)	530 (10.6)	134 (2.7)	<0.001	827 (8.4)	155 (22.1)	97 (51.1)
B2M (mg/dL)	3.6 (3.1)	2.2 (0.5)	1.9 (0.4)	<0.001	2.0 (0.6)	2.5 (1.7)	4.5 (5.1)
BTP (mg/L)	1.1 (0.9)	0.7 (0.2)	0.6 (0.3)	<0.001	0.7 (0.2)	0.8 (0.4)	1.4 (1.5)

Note: Unless otherwise indicated, values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation or median [interquartile range]. ACR, albumin-creatinine ratio; B2M, β2-microglobulin; BMI, body mass index; BTP, β-trace protein; CHD, coronary heart disease; eGFR_{cr}, creatinine-based estimated glomerular filtration rate; PPI, Proton pump inhibitor

[†] Diabetes defined by self-reported history of physician diagnosis, anti-diabetes medication use during past two weeks, fasting blood glucose 126 mg/dL or non-fasting blood glucose 200 mg/dL

* Hypertension defined by SBP 140 mm Hg, DBP 90 mm Hg, or self-reported hypertension medication use during past two weeks

** Number (percentage women).

*** At visit 3.

Table 2

Adjusted hazard ratios for fracture-related hospitalization

Variable	Unadjusted Model	Model 1	Model 2
eGFR _{Cr} , per 10 ml/min/1.73 m ² decrease			
<60 ml/min/1.73 m ²	1.34 ^{***} (1.15, 1.56)	1.49 ^{***} (1.27, 1.75)	1.24 [*] (1.05, 1.47)
60 ml/min/1.73 m ²	1.09 ^{**} (1.03, 1.15)	0.94 (0.89, 1.00)	0.96 (0.91, 1.03)
Age, per 10-y older		2.35 ^{***} (2.04, 2.71)	2.25 ^{***} (1.94, 2.60)
Female sex		1.50 ^{***} (1.29, 1.75)	1.46 ^{***} (1.25, 1.72)
Race and center White			
North Carolina		1.00 (reference)	1.00 (reference)
Minnesota		0.91 (0.76, 1.10)	0.93 (0.77, 1.13)
Maryland		0.68 ^{***} (0.56, 0.83)	0.69 ^{***} (0.56, 0.85)
Black			
North Carolina		0.58 (0.32, 1.03)	0.56 (0.31, 1.00)
Mississippi		0.51 ^{***} (0.40, 0.66)	0.53 ^{***} (0.41, 0.68)
ACR, per two-fold increase			1.10 ^{***} (1.06, 1.14)
BMI, per 5-kg/m ² higher			
<30 mg/g			0.94 (0.82, 1.08)
30 mg/g			1.04 (0.91, 1.18)
Diabetes			1.25 [*] (1.02, 1.54)
Smoking			1.43 ^{***} (1.17, 1.76)
Prevalent CHD			1.25 (0.97, 1.61)
Glucocorticoid Use			2.10 ^{***} (1.45, 3.04)
Bisphosphonate Use			2.44 ^{***} (1.53, 3.90)
PPI Use			1.43 [*] (1.00, 2.03)

Note: Values are given as adjusted HR (95% confidence interval). Model 1: Demographically adjusted HRs. Model 2: Fully adjusted HRs.

ACR, albumin-creatinine ratio; BMI, body mass index; CHD, coronary heart disease; eGFR_{Cr}, creatinine-based estimated glomerular filtration rate; HR, hazard ratio; PPI, proton pump inhibitor

* p 0.05,

** p 0.01,

*** p 0.001

Table 3

Association of alternative filtration markers with fracture hospitalization with and without adjustment for eGFR_{cr}

Alternative filtration marker	Without eGFR _{cr} adjustment	With eGFR _{cr} adjustment
eGFR _{cys} [^]	1.15 *** (1.06–1.25)	1.22 *** (1.11–1.35)
1/B2M ^{^^}	1.26 *** (1.15–1.37)	1.37 *** (1.24–1.51)
1/BTP ^{^^^}	1.09 * (1.00–1.19)	1.13 * (1.02–1.25)

Note: Values are given as hazard ratio (95% confidence interval); hazard ratios express the risk associated with 1-SD decrease. Adjusted for age, gender, race and center, body mass index, diabetes status, cigarette smoking, prevalent coronary heart disease, bisphosphonate use, proton pump inhibitor use, glucocorticoid use, and albumin-creatinine ratio levels. We tested the linearity assumption for alternative filtration markers and there was no deviation from linearity.

B2M, β_2 -microglobulin; BMI, body mass index; BTP, β -trace protein; eGFR_{cr}, creatinine-based estimated glomerular filtration rate; SD, standard deviation

[^]SD= 18.32

^{^^}SD =0.12.

^{^^^}SD=0.36

* p 0.05,

** p 0.01,

*** p 0.001

Table 4

Adjusted hazard ratios of fracture-related hospitalization according to CKD status classified by eGFR_{cys} and eGFR_{cr}.

	eGFR _{cr} <60 ml/min/1.73 m ²	
	No	Yes
eGFR _{cys} <60 ml/min/1.73 m ²		
No	1.00 (reference)	0.89 (0.56–1.41)
Yes	1.53 ^{***} (1.19–1.97)	1.45 [*] (1.05–2.00)

Note; Values are given as adjusted hazard ratio (95% confidence interval). Adjusted for age, gender, race and center, body mass index, diabetes status, cigarette smoking, prevalent coronary heart disease, bisphosphonate use, proton pump inhibitor use, glucocorticoid use, and albumin-creatinine ratio levels.

eGFR_{cr}, creatinine-based estimated glomerular filtration rate; eGFR_{cys}, cystatin C-based estimated glomerular filtration rate; CKD, chronic kidney disease

*
p 0.05,

**
p 0.01

p 0.001