Lim, W.H., Lewis, J.R., Wong, G., Dogra, G.K., Zhu, K., Lim, E.M., Dhaliwal, S.S. & Prince, R.L. (2013). Five-year decline in estimated glomerular filtration rate associated with a higher risk of renal disease and atherosclerotic vascular disease clinical events in elderly women. QJM, 106(5), 443-450.

QJM: An International Journal of Medicine

Five-Year Decline In Estimated Glomerular Filtration Rate Associated With A Higher Risk Of Renal Disease And Atherosclerotic Vascular Disease Clinical Events In Elderly Women

Journal:	*QJM: An International Journal of Medicine*
Manuscript ID:	QJM-2012-083.R1
Manuscript Type:	Original Article
Date Submitted by the Author:	n/a
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Keywords:	Nephrology, Epidemiology, Cardiovascular disease

Five-Year Decline In Estimated Glomerular Filtration Rate Associated With A Higher Risk Of Renal Disease And Atherosclerotic Vascular Disease Clinical Events In Elderly Women

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Short title: GFR decline and renal disease and ASVD

Word count: Abstract 226, Body 2,636 ***Tables:*** 4

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The University of Western Australia Human Ethics Committee had approved the study and written informed consents were obtained from all participants.

Abstract

Background: Estimated glomerular filtration rate (eGFR) has been demonstrated to predict atherosclerotic vascular disease (ASVD)-associated clinical events independent of traditional vascular risk factors. Recent studies have demonstrated that eGFR decline over time may improve prediction of ASVD-associated mortality risk in chronic kidney disease (CKD) patients. ***Aim***: The aim of this study is to evaluate the association between 5-year change in eGFR with renal disease and ASVD-associated clinical events. ***Design***: Prospective observational study. ***Methods***: 1,012 women over the age of 70 from the Calcium Intake Fracture Outcome Study were included. Baseline characteristics including baseline and 5-year creatinine, participants' comorbidities and complete verified 10-year records for ASVD and renal disease-associated hospitalization and/or mortality were obtained using the Western Australian Data Linkage System. ***Results***: Participants were stratified according to annual rate of eGFR change in quartiles (≤-1.2 [first quartile], >-1.2-0.1 [second quartile], >0.1-1.7 [third quartile] and >1.7ml/min/1.73m^2 year [fourth quartile]). In the adjusted model, compared with participants in the fourth quartile, those in the first and/or second quartiles of annual eGFR change had significantly higher risk of renal disease and/or ASVD-associated clinical events. However, the association with renal clinical events was more apparent in participants with baseline eGFR of <60mL/min/1.73m^2. ***Conclusion***: The results of this study suggest that the inclusion of long-term eGFR change over time might augment prognostication for renal disease and ASVD-associated clinical events in elderly women.

Key words: Glomerular filtration rate, renal disease, mortality, atherosclerotic vascular disease

Introduction

Patients with chronic kidney disease (CKD) are at an increased risk of end-stage kidney disease (ESKD), cardiovascular disease-related clinical events and all-cause mortality, especially when estimated glomerular filtration rate (eGFR) is less than 60 mL/min/1.73m^2 [1-5]. There is also evidence that the association between eGFR and mortality is J-shaped with increased risk for individuals with eGFR values of <75 and ≥120mL/min/1.73m^2 [6]. The predictive ability of eGFR for adverse clinical events appears to be independent of traditional vascular risk factors and across all age groups, but particularly in elderly individuals [7,8]. Multiple prediction equations to estimate GFR have been developed and the recently published equation from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) may be a more reliable marker of GFR and appeared to be superior compared to Modification of Diet in Renal Disease (MDRD) or Cockcroft-Gault equations in categorizing individuals with respect to long-term risk of adverse clinical outcomes, including mortality and stroke [9-12]. Establishing rate of eGFR change over time in individuals with mild to moderate CKD may further enhance prediction of athero-thrombotic and mortality risk in this group of patients [13-15]. However, the association between longer-term changes in eGFR and the risk of adverse clinical events remains unclear.

The aim of this study is to evaluate the association between the 5-year change in eGFR with 10-year renal disease and atherosclerotic vascular disease (ASVD)-associated clinical outcomes in a large longitudinal cohort of elderly women.

Subjects and Methods

Study Population

One thousand five hundred women were recruited in 1998 to a 5-year prospective, randomized, controlled trial of oral calcium supplements to prevent osteoporotic fractures, the Calcium Intake Fracture Outcome study (CAIFOS; Australian Clinical Trials Registry Registration Number: ACTRN012607000055404) [16]. In the subsequent 5 years following inclusion in the study, participants had received 1.2 g of elemental calcium daily or matching placebo. At the conclusion of CAIFOS, participants were included in a 5-year follow-up study. Baseline disease burden and medications were comparable between the participants and general population of similar age [16]. The University of Western Australia Human Ethics Committee had approved the study and written informed consents were obtained from all participants.

Baseline medical history and medications were obtained from all participants and participants' general practitioners verified the history and medications (including the type of anti-hypertensive medications) where possible. Baseline weight, height and blood pressure (average of three readings) were obtained at study inclusion.

Biochemistry

Fasting blood ~~and urine~~ samples were collected from the participants at baseline and at 5 years. Baseline creatinine were obtained from 1,313 women and tested in 2005, with 1,012 women having a second creatinine measurement at 5 years tested in 2011. Serum creatinine was analysed using an isotope dilution mass spectrometry (IDMS) traceable Jaffe kinetic assay for creatinine on a Hitachi 917 analyser (Roche Diagnostics GmbH, Mannheim Germany) for baseline samples or the Architect ci16200 analyser (Abbott) for 5-year samples. The correlation coefficient (r^2) between the machines was 0.998 with the Passing

and Bablok slope of 0.966 and the Passing and Bablok intercept of 6.16 (n=37). eGFR was calculated using the CKD-EPI formula, expressed as a single equation: eGFR = 141 × $\min(Scr/\kappa, 1)^{\alpha}$ × $\max(Scr/\kappa, 1)^{-1.209}$ × 0.993^{Age} × 1.018 [if female] × 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1 [10].

Baseline and follow-up renal failure-associated hospitalization and mortality

Baseline renal disease hospitalizations were collected between 1980 and 1998 using International Classification of Diseases, Injuries and Causes of Death Clinical Modification (ICD-9-CM) [17]. These codes included glomerular diseases (ICD-9-CM codes 580 – 583); renal tubulo-interstitial diseases (ICD-9-CM codes 593.3 – 593.5, 593.7); renal failure (ICD-9-CM codes 584 – 586); and hypertensive renal disease (ICD-9-CM code 403). The search for renal disease hospitalizations included any diagnosis code.

This study outcome was the presence of any acute or chronic renal disease events causing hospitalization and/or mortality. Renal disease hospitalizations were retrieved from the Western Australian Data Linkage System (WADLS) for each of the study participants from 1998 until 10 years subsequent to their baseline visit. Complete adjudicated hospitalization data for clinical events over 10 years was obtained using the WADLS. WADLS is a comprehensive, population-based linkage system connecting 40 years of data from over 30 health-related datasets for Western Australian residents coded using ICD codes [18]. The coded discharge diagnosis data included all public and private inpatient hospitalizations and deaths within Western Australia [18]. WADLS provides a complete validated record of every participant's primary diagnosis hospitalizations and cause of death from the coded records of the death certificate. Renal disease events were defined using

primary and additional diagnosis codes from ICD-9-CM [17] and the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10- AM) [19]. These codes included glomerular diseases (ICD-9-CM codes 580 – 583, ICD-10- AM codes N00-08); renal tubulo-interstitial diseases (ICD-9-CM codes 593.3 – 593.5, 593.7 and 590-591, ICD-10- AM codes N09-16); renal failure (ICD-9-CM codes 584 – 586, ICD-10- AM codes N17-19); and hypertensive renal disease (ICD-9-CM code 403, ICD-10- AM codes I12). The search for renal disease-associated death ICD codes included all available diagnostic information that comprised Parts 1 and 2 of the death certificate and the principal diagnosis in the inpatient data. All diagnosis text fields from the death certificate were used to ascertain the cause(s) of deaths where these data were not yet available from the WADLS.

Baseline and follow-up atherosclerotic vascular disease (ASVD) events were determined from the complete hospital discharge data from 1980-1998 and from 1998-2008 respectively and were defined using diagnosis codes from ICD-9-CM and ICD-10-AM. These codes included: ischemic heart disease (ICD-9-CM codes 410-414 and ICD-10-AM codes I20-I25); heart failure (ICD-9-CM code 428 and ICD-10-AM code I50); cerebrovascular disease excluding hemorrhage (ICD-9-CM codes 433-438 and ICD-10-AM codes I63-69, G45.9) and peripheral arterial disease (ICD-9-CM codes 440-444 and ICD-10-AM codes I70-74).

Statistical Analysis

Baseline characteristics were stratified by annual rate of eGFR change between baseline and 5 years in quartiles. Clinical correlates of eGFR change were assessed using forward stepwise linear regression models. Annual rate of eGFR change in quartiles were used to assess the association between eGFR change and clinical outcomes between 5 and 10

years following randomization, which was specified to be the odds ratio (OR) for renal failure-associated hospitalization and/or mortality and ASVD hospitalization and/or mortality adjusted for age, smoking history, baseline CKD-EPI eGFR, body mass index, systolic blood pressure, treated hypertension, diabetes, fasting cholesterol, baseline angiotensin-converting enzyme inhibitors (ACE-i), baseline statin, prevalent renal disease, prevalent ASVD and treatment code (i.e. calcium versus no calcium supplementation). P-values of less than 0.05 in two tailed testing were considered statistically significant. The data was analysed using SPSS (version 15; SPSS Inc, Chicago, IL).

Results

Baseline characteristics (Table1)

Participants were stratified into quartiles of annual rate of eGFR change (≤-1.2 [first quartile], >-1.2-0.1 [second quartile], >0.1-1.7 [third quartile] and >1.7ml/min/1.73m^2 year [fourth quartile]). Participants in the fourth quartile were less likely to have diabetes and were less likely to be maintained on anti-hypertensive medications compared to participants in the first and second quartiles. There was an inverse association between baseline eGFR and annual rate of eGFR change with participants in the fourth quartile having the lowest baseline eGFR but highest 5-year eGFR. BMI between baseline and 5-years was similar in all quartiles.

Association of clinical correlates of 5-year eGFR change (Table 2)

Baseline factors associated with 5-year change in CKD-EPI eGFR included age, smoking history, baseline CKD-EPI eGFR, body mass index, systolic blood pressure, treated hypertension and diabetes. There was no association between calcium supplementation, prevalent renal disease and prevalent ASVD with 5-year change in CKD-EPI eGFR.

Association of annual rate of eGFR change and 5-10 years clinical events (Table 3)

Compared to the fourth quartile of annual rate of eGFR change, participants in the first and second quartiles were at an increased risk of renal disease and/or ASVD-associated hospitalization and/or mortality in the age-adjusted and multivariable-adjusted models. There was no association between the use of calcium supplementation and ASVD-associated hospitalization and/or mortality. There was no association between long-term eGFR change and all-cause mortality.

Interaction between annual rate of eGFR change and baseline eGFR with 5-10years renal failure events (Table 4)

In the renal disease-associated clinical outcome model, there was an interaction between annual rate of eGFR change in quartiles and baseline eGFR. To investigate these further, participants were divided into eight groups, eGFR change in each quartile with baseline eGFR above and below 60mL/min/1.73m^2. In participants with baseline eGFR ≥60mL/min/1.73m^2, those within the first quartile of eGFR change had significantly higher risk of renal disease-associated clinical events compared to those in the fourth quartile. In participants with baseline eGFR of <60mL/min/1.73m^2, those within the first or second quartiles of eGFR change had significantly higher risk of renal disease-associated clinical events compared to those in the fourth quartile. There was no interaction between annual rate of eGFR change and baseline eGFR with respect to ASVD-associated clinical events.

Discussion

This study has demonstrated a robust association between long-term decline in eGFR and increased risk of renal disease and ASVD-associated hospitalisation and/or mortality in elderly women, especially in those with poorer baseline eGFR and independent of other known predictors of adverse clinical events.

Several studies have evaluated the effect of eGFR decline among older adults with and without CKD. A retrospective longitudinal study by *Al-Aly Z et al* of 4171 patients with rheumatoid arthritis and early stage 3 CKD (MDRD-derived eGFR of 45-60mL/min/1.73m^2) demonstrated that patients who experienced moderate and severe CKD progression (defined as eGFR loss of 1-4mL/min/1.73m^2 per year and loss of >4mL/min/1.73m^2 per year respectively) exhibited an increased risk of death (HR 1.10; 95% CI 0.95, 1.30 and HR 1.54, 95%CI 1.30, 1.82 respectively). In a retrospective cohort study of 15,465 elderly male and female stage 3-4 CKD patients (CKD-EPI-derived eGFR between 15-59mL/min/1.73m^2), *Perkins R et al* demonstrated that compared to stable eGFR group (median rate of eGFR change of -0.6mL/min per 1.73m^2/year), declining eGFR group (median rate of eGFR change of -4.8mL/min per 1.73m^2/year) had higher rates of hospital-acquired acute kidney injury (defined as an increase of 50% or more in serum creatinine during a hospitalization for any cause; rate of 76.2 vs 34.8 per 1000 patient-years) and community-acquired acute kidney injury (defined as an increase of 50% or more in serum creatinine during outpatient setting for any cause; rate of 38.6 vs 13.7 per 1000 patient-years). The authors also showed that patients with declining eGFR had a two-fold increase in the risk of death in the adjusted model, independent of prior episodes of acute kidney injury [14]. In a prospective cohort study of 17,026 Taiwanese patients age ≥50 years, *Cheng T et al* found that a 20% or greater decline in MDRD-derived eGFR from baseline was associated with over a two-fold increase in the risk of coronary artery disease and stroke, compared with those with <20% decline in

eGFR [20]. *Shilpak M et al* demonstrated in a longitudinal study of community-dwelling older adults that >3mL/min per year decline in cystatin C or MDRD-derived eGFR was associated with an increased risk of ischaemic heart disease among patients with or without CKD [21]. Similarly, our study has demonstrated that compared with participants with annual eGFR gain, participants with annual eGFR loss was associated with significantly higher risk of renal disease and ASVD-associated clinical events, especially those with poorer baseline eGFR (for renal disease clinical events) suggesting that the risk of renal disease clinical events are more likely in those with 'vulnerable' kidneys. Although the use of calcium supplementation has been shown to be associated with an 86% greater risk of myocardial infarction [22], a similar association with ASVD events was not observed in this study.

The association between increasing rate of eGFR change and adverse clinical events remains uncertain. In the studies by *Al-Aly Z et al* and *Perkins R et al* [13,14], patients who had increasing eGFR over time exhibited an increased risk of death compared to those with mild or stable CKD progression [13]. Unlike these studies, we did not find an association between increasing eGFR and adverse clinical outcomes. This difference in study findings may reflect dissimilar study populations with varying baseline comorbidities, the use of different eGFR prediction equations and/or differences in baseline eGFR. Unlike the study by *Al-Aly Z et al*, our study utilized CKD-EPI eGFR in the prediction model for clinical events, which has been shown to be superior compared to other eGFR equations in predicting long-term clinical risk, especially in females, [9]. Nevertheless, this association between increasing eGFR and outcome should be explored further.

Although it is well documented that eGFR invariably declines over time [23], a number of studies have demonstrated that eGFR may increase in a significant proportion of individuals, including those with pre-existing CKD. In the study by *Al-Aly Z et al*, 38% of predominantly elderly male rheumatoid arthritis patients with early stage 3 CKD exhibited a

mean eGFR increase of 3.5±3.6mL/min/year [13]. Similarly, in the study by *Perkins R et al*, over 30% of elderly male and female stage 3-4 CKD patients had shown an increase in eGFR over time with median increase of 3.5mL/min (interquartile range of 1.9-6.7mL/min) per year [14]. Our study has confirmed similar findings with up to 50% of elderly females exhibiting a similar increase in eGFR over time. Although the improvement in eGFR may reflect a decrease in creatinine as a result of loss of muscle mass, this was not apparent in our study as the BMI at baseline and at 5 years of individuals in the third and fourth quartiles was similar. However, individuals with improvement in eGFR were less likely to have diabetes or hypertension, both of which were risk factors for eGFR decline. It is plausible that participants in the first and second quartiles of eGFR change were hyperfiltrating, resulting in higher baseline eGFR compared to those in the higher quartiles of eGFR change. The availability of albuminuria and medications at 5 years may have helped to explore this issue further.

The mechanism explaining the association between the decline in renal function and the risk of renal disease and ASVD-associated hospitalisation and mortality remain uncertain. It is conceivable that eGFR change may represent a risk factor or marker of subclinical atherosclerosis, ventricular and vascular remodelling, oxidative stress, inflammation and/or activation of the renin-angiotensin system, all of which could potentially contribute to adverse clinical vascular events [20,24-26].

The strengths of this study include the complete and accurate data collection over a 10-year period in a large cohort of subjects. We were able to more accurately examine the association between eGFR change and clinical outcomes in the general population with minimal pre-existing atherosclerotic vascular and/or renal diseases, which further strengthens this association. Limitations include the inclusion of only female subjects, lack of radionuclide GFR measurements, availability of a single time-point creatinine to estimate

GFR at baseline and at 5 years and the lack of accurate data regarding medications at 5 years. The lack of association between prevalent renal disease and ASVD and 5-year change in eGFR is unexpected and may be explained by the relatively small proportion of participants with prevalent renal disease (1.5%) or ASVD (10.6%), the lack of information regarding the severity of those with prevalent diseases and potential random error may have contributed to our findings.

The results of this study suggest that the inclusion of eGFR change over time might augment prognostication for renal disease and ASVD-associated clinical events in elderly women, many of whom have stage 2-3 CKD at baseline. Future studies addressing the association between eGFR change and other markers of CKD including albuminuria as well as evaluating the effect of potential interventions to slow rate of eGFR deterioration on clinical outcomes are required.

Funding: The study was supported by Kidney Health Australia grant S07 10, Healthway Health Promotion Foundation of Western Australia and by project grants 254627, 303169 and 572604 from the National Health and Medical Research Council of Australia. The salary of JRL is supported by a Raine Medical Research Foundation Priming Grant. None of the funding agencies had any role in the conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Acknowledgement: The authors wish to thank the staff at the Data Linkage Branch, Hospital Morbidity Data Collection and Registry of Births, Deaths and Marriages for their work on providing the data for this study.

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Table 1: Baseline characteristics of study population stratified by 5-year change in CKD-EPI eGFR in quartiles.

	First quartile (n=253)	Second quartile (n=253)	Third quartile (n=253)	Fourth quartile (n=253)	Total (n=1012)
Annual rate of change in eGFR	≤ -1.2	> -1.2 to 0.1	>0.1 to 1.7	>1.7	-9.8 to 5.8
Age (years)*	75.3±2.6	75.3±2.8	75.0±2.5	74.6±2.5	75.0±2.6
Baseline BMI (kg/m^2)*	28.0±5.0	26.8±4.4	26.7±4.0	27.3±4.7	27.2±4.5
5 year BMI (kg/m^2)*	28.3±5.1	27.0±4.6	26.8±4.3	26.8±4.7	27.2±4.7
SBP (mmHg)*	141.0±18.8	137.9±17.4	135.7±18.3	135.3±17.3	137.5±18.1
DBP (mmHg)	73.1±11.1	73.2±10.1	73.1±11.	73.0±10.7	73.1±10.7
Smoking (yes)	104 (25.0%)	85 (33.9%)	92 (36.5%)	77 (30.4%)	358 (35.5%)
Anti-hypertensive medications (yes)	110 (43.5%)	101 (39.9%)	96 (37.9%)	84 (33.2%)	391 (38.6%)
Diabetes (yes)*	24 (9.5%)	14 (5.5%)	9 (3.6%)	10 (4.0%)	57 (5.6%)
Baseline ACE-i	48 (22.0%)	32 (14.7%)	35 (15.6%)	37 (15.7%)	152 (17.0%)
Baseline statin	45 (20.6%)	44 (20.3%)	37 (16.5%)	44 (18.6%)	170 (19.0%)
Cholesterol (mmol/L)	5.9±1.1	6.0±1.0	5.8±1.1	5.9±1.1	5.8±1.1
Prevalent renal disease (yes)	6 (2.4%)	2 (0.8%)	4 (1.6%)	3 (1.2%)	15 (1.5%)
Prevalent ASVD (yes)	25 (9.9%)	29 (11.5%)	23 (9.1%)	30 (11.9%)	107 (10.6%)
Baseline CKD-EPI eGFR (ml/min/1.73m2)*	70.4±13.0	70.8±15.8	64.9±11.8	59.6±8.3	66.4±13.3
5-year CKD-EPI eGFR (ml/min/1.73m2)*	56.3±15.3	68.2±15.5	69.2±11.7	73.0±8.2	66.6±14.4

*Data expressed as proportion (number and %) or mean ± SD or interquartile range. *p<0.05 by ANOVA or chi squared test; BMI – body mass index, mmHg - millimetres mercury, ASVD – atherosclerotic vascular disease, CKD-EPI eGFR – Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate, SBP – systolic blood pressure, DBP – diastolic blood pressure, ACE-I – angiotensin-converting enzyme inhibitor.*

Table 2: Baseline clinical correlates of five-year change in CKD-EPI eGFR.

	Standardized β coefficient	P value
Age (years)	-0.081	0.010
BMI (kg/m^2)	-0.067	0.033
Systolic blood pressure (mm/Hg)	-0.112	<0.001
Anti-hypertensive medications (yes)	-0.100	0.001
Baseline ACE-I (yes)	~~-0.086~~ 0.803	~~0.006~~0.484
Baseline statin (yes)	-0.670	0.501
Cholesterol (mmol/L)	0.155	0.662
Calcium (yes)	-1.073	0.113
Smoked ever (yes)	-0.086	0.006
Diabetes (yes)	-0.099	0.002
Baseline CKD-EPI eGFR	-0.111	<0.001
Prevalent ASVD (yes)	0.001	0.964
Prevalent renal disease (yes)	-0.014	0.654

Data expressed as the standardized regression coefficients (with corresponding p-values in brackets). The coefficient indicates the increase in per unit increment for continuous variables; for binary traits, this corresponds to the absence or presence of the trait. BMI – body mass index, mmHg, millimetres mercury, SBP – systolic blood pressure, DBP – diastolic blood pressure, ASVD – atherosclerotic vascular disease, CKD-EPI eGFR - Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate, ACE-I = angiotensin converting enzyme inhibitor.

Table 3: Risk of adverse clinical outcomes according to 5-year change in CKD-EPI in quartiles.

Events		OR (95% CI)	P value
Renal disease hospitalization or death			
(n=56 events)			
Age-adjusted			
	First quartile	8.02 (3.06, 20.98)	<0.001
	Second quartile	3.36 (1.20, 9.41)	0.021
	Third quartile	2.25 (0.77, 6.57)	0.139
	Fourth quartile	1.00	
Multivariable-adjusted			
	First quartile	15.19 (5.24, 44.05)	<0.001
	Second quartile	4.04 (1.33, 12.33)	0.014
	Third quartile	2.68 (0.88, 8.23)	0.084
	Fourth quartile	1.00	
Any ASVD hospitalization or mortality			
(n=179 events)			
Age-adjusted			
	First quartile	2.06 (1.30, 3.27)	0.002
	Second quartile	0.98 (0.59, 1.62)	0.929
	Third quartile	1.36 (0.85, 2.19)	0.196
	Fourth quartile	1.00	
Multivariable-adjusted			
	First quartile	2.15 (1.25, 3.70)	0.006
	Second quartile	1.15 (0.65, 2.02)	0.631
	Third quartile	1.49 (0.89, 2.49)	0.131
	Fourth quartile	1.00	

Data expressed as odds ratio and 95%CI. Multivariate models adjusted for age, body mass index, baseline CKD-EPI eGFR, smoking history, diabetes, treatment code, systolic blood pressure, diastolic blood pressure, use of anti-hypertensive medication at baseline, treatment code and prevalent renal and ASVD diseases.

Table 4: Risk of renal failure hospitalization and/or mortality according to 5-year change in CKD-EPI in quartiles stratified by baseline CKD-EPI eGFR above and below 60mL/min/1.73m^2.

Events	Number (%)	OR (95% CI)	P value
Renal disease hospitalization/death			
Multivariable-adjusted			
First quartile + eGFR ≥60mL/min	19/192(10%)	**5.95 (1.33, 26.50)**	**0.019**
Second quartile + eGFR ≥60mL/min	7/187 (4%)	2.88 (0.58, 14.27)	0.195
Third quartile + eGFR ≥60mL/min	7/181 (4%)	2.62 (0.52, 13.06)	0.240
Fourth quartile + eGFR ≥60mL/min	2/125 (2%)	1.00	
First quartile + eGFR <60mL/min	25/61 (41%)	**14.99 (5.25, 42.81)**	**<0.001**
Second quartile + eGFR <60mL/min	13/66 (20%)	**4.26 (1.38, 13.12)**	**0.012**
Third quartile + eGFR <60mL/min	8/72 (11%)	3.11 (0.96, 10.05)	0.058
Fourth quartile + eGFR <60mL/min	5/128 (4%)	1.00	

Data expressed as event rate (number/%), odds ratio and 95%CI. Multivariate models adjusted for baseline age, body mass index, smoking history, diabetes, calcium treatment code, systolic blood pressure, use of anti-hypertensive medication, treatment code and prevalent renal disease and ASVD

Five-Year Decline In Estimated Glomerular Filtration Rate Associated With A Higher Risk Of Renal Disease And Atherosclerotic Vascular Disease Clinical Events In Elderly Women

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Short title: GFR decline and renal disease and ASVD

Word count: Abstract 226, Body 2,636 ***Tables:*** 4

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The University of Western Australia Human Ethics Committee had approved the study and written informed consents were obtained from all participants.

Abstract

Background: Estimated glomerular filtration rate (eGFR) has been demonstrated to predict atherosclerotic vascular disease (ASVD)-associated clinical events independent of traditional vascular risk factors. Recent studies have demonstrated that eGFR decline over time may improve prediction of ASVD-associated mortality risk in chronic kidney disease (CKD) patients. ***Aim***: The aim of this study is to evaluate the association between 5-year change in eGFR with renal disease and ASVD-associated clinical events. ***Design***: Prospective observational study. ***Methods***: 1,012 women over the age of 70 from the Calcium Intake Fracture Outcome Study were included. Baseline characteristics including baseline and 5-year creatinine, participants' comorbidities and complete verified 10-year records for ASVD and renal disease-associated hospitalization and/or mortality were obtained using the Western Australian Data Linkage System. ***Results***: Participants were stratified according to annual rate of eGFR change in quartiles (≤-1.2 [first quartile], >-1.2-0.1 [second quartile], >0.1-1.7 [third quartile] and >1.7ml/min/1.73m^2 year [fourth quartile]). In the adjusted model, compared with participants in the fourth quartile, those in the first and/or second quartiles of annual eGFR change had significantly higher risk of renal disease and/or ASVD-associated clinical events. However, the association with renal clinical events was more apparent in participants with baseline eGFR of <60mL/min/1.73m^2. ***Conclusion***: The results of this study suggest that the inclusion of long-term eGFR change over time might augment prognostication for renal disease and ASVD-associated clinical events in elderly women.

Key words: Glomerular filtration rate, renal disease, mortality, atherosclerotic vascular disease

Introduction

Patients with chronic kidney disease (CKD) are at an increased risk of end-stage kidney disease (ESKD), cardiovascular disease-related clinical events and all-cause mortality, especially when estimated glomerular filtration rate (eGFR) is less than 60 mL/min/1.73m^2 [1-5]. There is also evidence that the association between eGFR and mortality is J-shaped with increased risk for individuals with eGFR values of <75 and ≥120mL/min/1.73m^2 [6]. The predictive ability of eGFR for adverse clinical events appears to be independent of traditional vascular risk factors and across all age groups, but particularly in elderly individuals [7,8]. Multiple prediction equations to estimate GFR have been developed and the recently published equation from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) may be a more reliable marker of GFR and appeared to be superior compared to Modification of Diet in Renal Disease (MDRD) or Cockcroft-Gault equations in categorizing individuals with respect to long-term risk of adverse clinical outcomes, including mortality and stroke [9-12]. Establishing rate of eGFR change over time in individuals with mild to moderate CKD may further enhance prediction of athero-thrombotic and mortality risk in this group of patients [13-15]. However, the association between longer-term changes in eGFR and the risk of adverse clinical events remains unclear.

The aim of this study is to evaluate the association between the 5-year change in eGFR with 10-year renal disease and atherosclerotic vascular disease (ASVD)-associated clinical outcomes in a large longitudinal cohort of elderly women.

Subjects and Methods

Study Population

One thousand five hundred women were recruited in 1998 to a 5-year prospective, randomized, controlled trial of oral calcium supplements to prevent osteoporotic fractures, the Calcium Intake Fracture Outcome study (CAIFOS; Australian Clinical Trials Registry Registration Number: ACTRN012607000055404) [16]. In the subsequent 5 years following inclusion in the study, participants had received 1.2 g of elemental calcium daily or matching placebo. At the conclusion of CAIFOS, participants were included in a 5-year follow-up study. Baseline disease burden and medications were comparable between the participants and general population of similar age [16]. The University of Western Australia Human Ethics Committee had approved the study and written informed consents were obtained from all participants.

Baseline medical history and medications were obtained from all participants and participants' general practitioners verified the history and medications (including the type of anti-hypertensive medications) where possible. Baseline weight, height and blood pressure (average of three readings) were obtained at study inclusion.

Biochemistry

Fasting blood samples were collected from the participants at baseline and at 5 years. Baseline creatinine were obtained from 1,313 women and tested in 2005, with 1,012 women having a second creatinine measurement at 5 years tested in 2011. Serum creatinine was analysed using an isotope dilution mass spectrometry (IDMS) traceable Jaffe kinetic assay for creatinine on a Hitachi 917 analyser (Roche Diagnostics GmbH, Mannheim Germany) for baseline samples or the Architect ci16200 analyser (Abbott) for 5-year samples. The correlation coefficient (r^2) between the machines was 0.998 with the Passing and Bablok

slope of 0.966 and the Passing and Bablok intercept of 6.16 (n=37). eGFR was calculated using the CKD-EPI formula, expressed as a single equation: $eGFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1 [10].

Baseline and follow-up renal failure-associated hospitalization and mortality

Baseline renal disease hospitalizations were collected between 1980 and 1998 using International Classification of Diseases, Injuries and Causes of Death Clinical Modification (ICD-9-CM) [17]. These codes included glomerular diseases (ICD-9-CM codes 580 – 583); renal tubulo-interstitial diseases (ICD-9-CM codes 593.3 – 593.5, 593.7); renal failure (ICD-9-CM codes 584 – 586); and hypertensive renal disease (ICD-9-CM code 403). The search for renal disease hospitalizations included any diagnosis code.

This study outcome was the presence of any acute or chronic renal disease events causing hospitalization and/or mortality. Renal disease hospitalizations were retrieved from the Western Australian Data Linkage System (WADLS) for each of the study participants from 1998 until 10 years subsequent to their baseline visit. Complete adjudicated hospitalization data for clinical events over 10 years was obtained using the WADLS. WADLS is a comprehensive, population-based linkage system connecting 40 years of data from over 30 health-related datasets for Western Australian residents coded using ICD codes [18]. The coded discharge diagnosis data included all public and private inpatient hospitalizations and deaths within Western Australia [18]. WADLS provides a complete validated record of every participant's primary diagnosis hospitalizations and cause of death from the coded records of the death certificate. Renal disease events were defined using

primary and additional diagnosis codes from ICD-9-CM [17] and the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10- AM) [19]. These codes included glomerular diseases (ICD-9-CM codes 580 – 583, ICD-10- AM codes N00-08); renal tubulo-interstitial diseases (ICD-9-CM codes 593.3 – 593.5, 593.7 and 590-591, ICD-10- AM codes N09-16); renal failure (ICD-9-CM codes 584 – 586, ICD-10- AM codes N17-19); and hypertensive renal disease (ICD-9-CM code 403, ICD-10- AM codes I12). The search for renal disease-associated death ICD codes included all available diagnostic information that comprised Parts 1 and 2 of the death certificate and the principal diagnosis in the inpatient data. All diagnosis text fields from the death certificate were used to ascertain the cause(s) of deaths where these data were not yet available from the WADLS.

Baseline and follow-up atherosclerotic vascular disease (ASVD) events were determined from the complete hospital discharge data from 1980-1998 and from 1998-2008 respectively and were defined using diagnosis codes from ICD-9-CM and ICD-10-AM. These codes included: ischemic heart disease (ICD-9-CM codes 410-414 and ICD-10-AM codes I20-I25); heart failure (ICD-9-CM code 428 and ICD-10-AM code I50); cerebrovascular disease excluding hemorrhage (ICD-9-CM codes 433-438 and ICD-10-AM codes I63-69, G45.9) and peripheral arterial disease (ICD-9-CM codes 440-444 and ICD-10-AM codes I70-74).

Statistical Analysis

Baseline characteristics were stratified by annual rate of eGFR change between baseline and 5 years in quartiles. Clinical correlates of eGFR change were assessed using forward stepwise linear regression models. Annual rate of eGFR change in quartiles were used to assess the association between eGFR change and clinical outcomes between 5 and 10

years following randomization, which was specified to be the odds ratio (OR) for renal failure-associated hospitalization and/or mortality and ASVD hospitalization and/or mortality adjusted for age, smoking history, baseline CKD-EPI eGFR, body mass index, systolic blood pressure, treated hypertension, diabetes, fasting cholesterol, baseline angiotensin-converting enzyme inhibitors (ACE-i), baseline statin, prevalent renal disease, prevalent ASVD and treatment code (i.e. calcium versus no calcium supplementation). P-values of less than 0.05 in two tailed testing were considered statistically significant. The data was analysed using SPSS (version 15; SPSS Inc, Chicago, IL).

Results

Baseline characteristics (Table1)

Participants were stratified into quartiles of annual rate of eGFR change (≤-1.2 [first quartile], >-1.2-0.1 [second quartile], >0.1-1.7 [third quartile] and >1.7ml/min/1.73m^2 year [fourth quartile]). Participants in the fourth quartile were less likely to have diabetes and were less likely to be maintained on anti-hypertensive medications compared to participants in the first and second quartiles. There was an inverse association between baseline eGFR and annual rate of eGFR change with participants in the fourth quartile having the lowest baseline eGFR but highest 5-year eGFR. BMI between baseline and 5-years was similar in all quartiles.

Association of clinical correlates of 5-year eGFR change (Table 2)

Baseline factors associated with 5-year change in CKD-EPI eGFR included age, smoking history, baseline CKD-EPI eGFR, body mass index, systolic blood pressure, treated hypertension and diabetes. There was no association between calcium supplementation, prevalent renal disease and prevalent ASVD with 5-year change in CKD-EPI eGFR.

Association of annual rate of eGFR change and 5-10 years clinical events (Table 3)

Compared to the fourth quartile of annual rate of eGFR change, participants in the first and second quartiles were at an increased risk of renal disease and/or ASVD-associated hospitalization and/or mortality in the age-adjusted and multivariable-adjusted models. There was no association between the use of calcium supplementation and ASVD-associated hospitalization and/or mortality. There was no association between long-term eGFR change and all-cause mortality.

Interaction between annual rate of eGFR change and baseline eGFR with 5-10years renal failure events (Table 4)

In the renal disease-associated clinical outcome model, there was an interaction between annual rate of eGFR change in quartiles and baseline eGFR. To investigate these further, participants were divided into eight groups, eGFR change in each quartile with baseline eGFR above and below 60mL/min/1.73m^2. In participants with baseline eGFR ≥60mL/min/1.73m^2, those within the first quartile of eGFR change had significantly higher risk of renal disease-associated clinical events compared to those in the fourth quartile. In participants with baseline eGFR of <60mL/min/1.73m^2, those within the first or second quartiles of eGFR change had significantly higher risk of renal disease-associated clinical events compared to those in the fourth quartile. There was no interaction between annual rate of eGFR change and baseline eGFR with respect to ASVD-associated clinical events.

Discussion

This study has demonstrated a robust association between long-term decline in eGFR and increased risk of renal disease and ASVD-associated hospitalisation and/or mortality in elderly women, especially in those with poorer baseline eGFR and independent of other known predictors of adverse clinical events.

Several studies have evaluated the effect of eGFR decline among older adults with and without CKD. A retrospective longitudinal study by *Al-Aly Z et al* of 4171 patients with rheumatoid arthritis and early stage 3 CKD (MDRD-derived eGFR of 45-60mL/min/1.73m^2) demonstrated that patients who experienced moderate and severe CKD progression (defined as eGFR loss of 1-4mL/min/1.73m^2 per year and loss of >4mL/min/1.73m^2 per year respectively) exhibited an increased risk of death (HR 1.10; 95% CI 0.95, 1.30 and HR 1.54, 95%CI 1.30, 1.82 respectively). In a retrospective cohort study of 15,465 elderly male and female stage 3-4 CKD patients (CKD-EPI-derived eGFR between 15-59mL/min/1.73m^2), *Perkins R et al* demonstrated that compared to stable eGFR group (median rate of eGFR change of -0.6mL/min per 1.73m^2/year), declining eGFR group (median rate of eGFR change of -4.8mL/min per 1.73m^2/year) had higher rates of hospital-acquired acute kidney injury (defined as an increase of 50% or more in serum creatinine during a hospitalization for any cause; rate of 76.2 vs 34.8 per 1000 patient-years) and community-acquired acute kidney injury (defined as an increase of 50% or more in serum creatinine during outpatient setting for any cause; rate of 38.6 vs 13.7 per 1000 patient-years). The authors also showed that patients with declining eGFR had a two-fold increase in the risk of death in the adjusted model, independent of prior episodes of acute kidney injury [14]. In a prospective cohort study of 17,026 Taiwanese patients age ≥50 years, *Cheng T et al* found that a 20% or greater decline in MDRD-derived eGFR from baseline was associated with over a two-fold increase in the risk of coronary artery disease and stroke, compared with those with <20% decline in

eGFR [20]. *Shilpak M et al* demonstrated in a longitudinal study of community-dwelling older adults that >3mL/min per year decline in cystatin C or MDRD-derived eGFR was associated with an increased risk of ischaemic heart disease among patients with or without CKD [21]. Similarly, our study has demonstrated that compared with participants with annual eGFR gain, participants with annual eGFR loss was associated with significantly higher risk of renal disease and ASVD-associated clinical events, especially those with poorer baseline eGFR (for renal disease clinical events) suggesting that the risk of renal disease clinical events are more likely in those with 'vulnerable' kidneys. Although the use of calcium supplementation has been shown to be associated with an 86% greater risk of myocardial infarction [22], a similar association with ASVD events was not observed in this study.

The association between increasing rate of eGFR change and adverse clinical events remains uncertain. In the studies by *Al-Aly Z et al* and *Perkins R et al* [13,14], patients who had increasing eGFR over time exhibited an increased risk of death compared to those with mild or stable CKD progression [13]. Unlike these studies, we did not find an association between increasing eGFR and adverse clinical outcomes. This difference in study findings may reflect dissimilar study populations with varying baseline comorbidities, the use of different eGFR prediction equations and/or differences in baseline eGFR. Unlike the study by *Al-Aly Z et al*, our study utilized CKD-EPI eGFR in the prediction model for clinical events, which has been shown to be superior compared to other eGFR equations in predicting long-term clinical risk, especially in females, [9]. Nevertheless, this association between increasing eGFR and outcome should be explored further.

Although it is well documented that eGFR invariably declines over time [23], a number of studies have demonstrated that eGFR may increase in a significant proportion of individuals, including those with pre-existing CKD. In the study by *Al-Aly Z et al*, 38% of predominantly elderly male rheumatoid arthritis patients with early stage 3 CKD exhibited a

mean eGFR increase of 3.5±3.6mL/min/year [13]. Similarly, in the study by *Perkins R et al*, over 30% of elderly male and female stage 3-4 CKD patients had shown an increase in eGFR over time with median increase of 3.5mL/min (interquartile range of 1.9-6.7mL/min) per year [14]. Our study has confirmed similar findings with up to 50% of elderly females exhibiting a similar increase in eGFR over time. Although the improvement in eGFR may reflect a decrease in creatinine as a result of loss of muscle mass, this was not apparent in our study as the BMI at baseline and at 5 years of individuals in the third and fourth quartiles was similar. However, individuals with improvement in eGFR were less likely to have diabetes or hypertension, both of which were risk factors for eGFR decline. It is plausible that participants in the first and second quartiles of eGFR change were hyperfiltrating, resulting in higher baseline eGFR compared to those in the higher quartiles of eGFR change. The availability of albuminuria and medications at 5 years may have helped to explore this issue further.

The mechanism explaining the association between the decline in renal function and the risk of renal disease and ASVD-associated hospitalisation and mortality remain uncertain. It is conceivable that eGFR change may represent a risk factor or marker of subclinical atherosclerosis, ventricular and vascular remodelling, oxidative stress, inflammation and/or activation of the renin-angiotensin system, all of which could potentially contribute to adverse clinical vascular events [20,24-26].

The strengths of this study include the complete and accurate data collection over a 10-year period in a large cohort of subjects. We were able to more accurately examine the association between eGFR change and clinical outcomes in the general population with minimal pre-existing atherosclerotic vascular and/or renal diseases, which further strengthens this association. Limitations include the inclusion of only female subjects, lack of radionuclide GFR measurements, availability of a single time-point creatinine to estimate

GFR at baseline and at 5 years and the lack of accurate data regarding medications at 5 years. The lack of association between prevalent renal disease and ASVD and 5-year change in eGFR is unexpected and may be explained by the relatively small proportion of participants with prevalent renal disease (1.5%) or ASVD (10.6%), the lack of information regarding the severity of those with prevalent diseases and potential random error may have contributed to our findings.

The results of this study suggest that the inclusion of eGFR change over time might augment prognostication for renal disease and ASVD-associated clinical events in elderly women, many of whom have stage 2-3 CKD at baseline. Future studies addressing the association between eGFR change and other markers of CKD including albuminuria as well as evaluating the effect of potential interventions to slow rate of eGFR deterioration on clinical outcomes are required.

Funding: The study was supported by Kidney Health Australia grant S07 10, Healthway Health Promotion Foundation of Western Australia and by project grants 254627, 303169 and 572604 from the National Health and Medical Research Council of Australia. The salary of JRL is supported by a Raine Medical Research Foundation Priming Grant. None of the funding agencies had any role in the conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Acknowledgement: The authors wish to thank the staff at the Data Linkage Branch, Hospital Morbidity Data Collection and Registry of Births, Deaths and Marriages for their work on providing the data for this study.

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Table 1: Baseline characteristics of study population stratified by 5-year change in CKD-EPI eGFR in quartiles.

	First quartile (n=253)	Second quartile (n=253)	Third quartile (n=253)	Fourth quartile (n=253)	Total (n=1012)
Annual rate of change in eGFR	≤ -1.2	> -1.2 to 0.1	>0.1 to 1.7	>1.7	-9.8 to 5.8
Age (years)*	75.3±2.6	75.3±2.8	75.0±2.5	74.6±2.5	75.0±2.6
Baseline BMI (kg/m^2)*	28.0±5.0	26.8±4.4	26.7±4.0	27.3±4.7	27.2±4.5
5 year BMI (kg/m^2)*	28.3±5.1	27.0±4.6	26.8±4.3	26.8±4.7	27.2±4.7
SBP (mmHg)*	141.0±18.8	137.9±17.4	135.7±18.3	135.3±17.3	137.5±18.1
DBP (mmHg)	73.1±11.1	73.2±10.1	73.1±11.	73.0±10.7	73.1±10.7
Smoking (yes)	104 (25.0%)	85 (33.9%)	92 (36.5%)	77 (30.4%)	358 (35.5%)
Anti-hypertensive medications (yes)	110 (43.5%)	101 (39.9%)	96 (37.9%)	84 (33.2%)	391 (38.6%)
Diabetes (yes)*	24 (9.5%)	14 (5.5%)	9 (3.6%)	10 (4.0%)	57 (5.6%)
Baseline ACE-i	48 (22.0%)	32 (14.7%)	35 (15.6%)	37 (15.7%)	152 (17.0%)
Baseline statin	45 (20.6%)	44 (20.3%)	37 (16.5%)	44 (18.6%)	170 (19.0%)
Cholesterol (mmol/L)	5.9±1.1	6.0±1.0	5.8±1.1	5.9±1.1	5.8±1.1
Prevalent renal disease (yes)	6 (2.4%)	2 (0.8%)	4 (1.6%)	3 (1.2%)	15 (1.5%)
Prevalent ASVD (yes)	25 (9.9%)	29 (11.5%)	23 (9.1%)	30 (11.9%)	107 (10.6%)
Baseline CKD-EPI eGFR (ml/min/1.73m2)*	70.4±13.0	70.8±15.8	64.9±11.8	59.6±8.3	66.4±13.3
5-year CKD-EPI eGFR (ml/min/1.73m2)*	56.3±15.3	68.2±15.5	69.2±11.7	73.0±8.2	66.6±14.4

*Data expressed as proportion (number and %) or mean ±SD or interquartile range. *p<0.05 by ANOVA or chi squared test; BMI – body mass index, mmHg - millimetres mercury, ASVD – atherosclerotic vascular disease, CKD-EPI eGFR – Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate, SBP – systolic blood pressure, DBP – diastolic blood pressure, ACE-I – angiotensin-converting enzyme inhibitor.*

Table 2: Baseline clinical correlates of five-year change in CKD-EPI eGFR.

	Standardized β coefficient	P value
Age (years)	-0.081	0.010
BMI (kg/m^2)	-0.067	0.033
Systolic blood pressure (mm/Hg)	-0.112	<0.001
Anti-hypertensive medications (yes)	-0.100	0.001
Baseline ACE-I (yes)	0.803	0.484
Baseline statin (yes)	-0.670	0.501
Cholesterol (mmol/L)	0.155	0.662
Calcium (yes)	-1.073	0.113
Smoked ever (yes)	-0.086	0.006
Diabetes (yes)	-0.099	0.002
Baseline CKD-EPI eGFR	-0.111	<0.001
Prevalent ASVD (yes)	0.001	0.964
Prevalent renal disease (yes)	-0.014	0.654

Data expressed as the standardized regression coefficients (with corresponding p-values in brackets). The coefficient indicates the increase in per unit increment for continuous variables; for binary traits, this corresponds to the absence or presence of the trait. BMI – body mass index, mmHg, millimetres mercury, SBP – systolic blood pressure, DBP – diastolic blood pressure, ASVD – atherosclerotic vascular disease, CKD-EPI eGFR - Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate, ACE-I = angiotensin converting enzyme inhibitor.

Table 3: Risk of adverse clinical outcomes according to 5-year change in CKD-EPI in quartiles.

Events		OR (95% CI)	P value
Renal disease hospitalization or death			
(n=56 events)			
Age-adjusted			
	First quartile	8.02 (3.06, 20.98)	<0.001
	Second quartile	3.36 (1.20, 9.41)	0.021
	Third quartile	2.25 (0.77, 6.57)	0.139
	Fourth quartile	1.00	
Multivariable-adjusted			
	First quartile	15.19 (5.24, 44.05)	<0.001
	Second quartile	4.04 (1.33, 12.33)	0.014
	Third quartile	2.68 (0.88, 8.23)	0.084
	Fourth quartile	1.00	
Any ASVD hospitalization or mortality			
(n=179 events)			
Age-adjusted			
	First quartile	2.06 (1.30, 3.27)	0.002
	Second quartile	0.98 (0.59, 1.62)	0.929
	Third quartile	1.36 (0.85, 2.19)	0.196
	Fourth quartile	1.00	
Multivariable-adjusted			
	First quartile	2.15 (1.25, 3.70)	0.006
	Second quartile	1.15 (0.65, 2.02)	0.631
	Third quartile	1.49 (0.89, 2.49)	0.131
	Fourth quartile	1.00	

Data expressed as odds ratio and 95%CI. Multivariate models adjusted for age, body mass index, baseline CKD-EPI eGFR, smoking history, diabetes, treatment code, systolic blood pressure, diastolic blood pressure, use of anti-hypertensive medication at baseline, treatment code and prevalent renal and ASVD diseases.

Table 4: Risk of renal failure hospitalization and/or mortality according to 5-year change in CKD-EPI in quartiles stratified by baseline CKD-EPI eGFR above and below 60mL/min/1.73m^2.

Events	Number (%)	OR (95% CI)	P value
Renal disease hospitalization/death			
Multivariable-adjusted			
First quartile + eGFR ≥60mL/min	19/192(10%)	**5.95 (1.33, 26.50)**	**0.019**
Second quartile + eGFR ≥60mL/min	7/187 (4%)	2.88 (0.58, 14.27)	0.195
Third quartile + eGFR ≥60mL/min	7/181 (4%)	2.62 (0.52, 13.06)	0.240
Fourth quartile + eGFR ≥60mL/min	2/125 (2%)	1.00	
First quartile + eGFR <60mL/min	25/61 (41%)	**14.99 (5.25, 42.81)**	**<0.001**
Second quartile + eGFR <60mL/min	13/66 (20%)	**4.26 (1.38, 13.12)**	**0.012**
Third quartile + eGFR <60mL/min	8/72 (11%)	3.11 (0.96, 10.05)	0.058
Fourth quartile + eGFR <60mL/min	5/128 (4%)	1.00	

Data expressed as event rate (number/%), odds ratio and 95%CI. Multivariate models adjusted for baseline age, body mass index, smoking history, diabetes, calcium treatment code, systolic blood pressure, use of anti-hypertensive medication, treatment code and prevalent renal disease and ASVD