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Kidney function, bone-mineral metabolism markers, and future risk of peripheral artery disease

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Abstract

Background and aims—Reduced kidney function is a risk factor for lower-extremity peripheral artery disease (PAD). However, the associations of novel filtration markers with PAD are yet to be quantified. Moreover, little is known on whether bone-mineral metabolism (BMM) markers are related to incident PAD beyond kidney function. *Methods:* Using data from 12,472 participants at baseline (1990–1992) of the Atherosclerosis Risk in Communities (ARIC) study, we comprehensively quantified the associations of kidney related markers with incident PAD (defined as hospitalizations with diagnosis of lower-extremity atherosclerosis, revascularization, or amputation). Kidney related markers of interest included estimated glomerular filtration rate (eGFR) (based on creatinine, cystatin C, and both), cystatin C, beta-2 microglobulin (B2M), and BMM markers (serum fibroblast growth factor 23, parathyroid hormone, calcium, and phosphorus).

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Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

C. Yang: conceived and designed the research; performed statistical analysis; drafted the manuscript; made critical revision of the manuscript for important intellectual content.

L. Kwak: performed statistical analysis.

S. Ballew, P. Garimella, B. Jaar, A. Folsom, E. Selvin, P. Lutsey, J. Coresh: interpreted the results; made critical revision of the manuscript for important intellectual content.

K. Matsushita: conceived and designed the research; performed statistical analysis; drafted the manuscript; handled funding and supervision; made critical revision of the manuscript for important intellectual content.

Results—During a median follow-up of 21 years, 471 participants developed incident PAD. Low eGFR was significantly associated with future PAD risk, with slightly stronger relationship when cystatin C was used (adjusted hazard ratio [HR] 6.3–8.3 for eGFR <30 and 2.4–3.5 for eGFR 30–59 *vs.* eGFR ⩾90 mL/min/1.73 m^2). Among all filtration markers, B2M had the strongest association with incident PAD (HR for top *vs.* bottom quartile 2.60 [95% CI: 1.91–3.54] for B2M *vs.* 1.20 [0.91–1.58] for creatinine-based eGFR). Among BMM markers, only phosphorus remained significant for PAD risk beyond potential confounders including kidney function (HR 1.47 [1.11–1.94] in top quartile).

Conclusions—Kidney dysfunction was independently associated with future PAD risk, particularly when assessed with cystatin C and B2M. Among the BMM markers tested, phosphorus was most robustly associated with incident PAD beyond kidney function. Our results suggest the potential usefulness of novel filtration markers for PAD risk assessment and the possible role of phosphorus in the pathophysiology of PAD.

1. Introduction

Peripheral artery disease (PAD), characterized by atherosclerosis of the lower extremities [1], affects more than 8 million adults in the U.S., increases the risk of adverse health outcomes [2], and is associated with reduced functional performance and high cost of health care [3, 4]. PAD is especially an important complication for those with chronic kidney disease (CKD), particularly at advanced stage [5, 6]. Indeed, the incidence rate of PAD is higher than that of myocardial infarction and stroke among dialysis patients [7]. Of note, mildly to moderately reduced kidney function has also been associated with higher risk of PAD in several reports [8–10].

Since those reports were published, new equations for estimated glomerular filtration rate (eGFR) (e.g., the CKD-EPI equations) and novel filtration markers (e.g., cystatin C and β2-microglobulin [B2M]) have demonstrated stronger associations with cardiovascular events as compared to the more traditional measure of kidney function, creatinine-based eGFR using MDRD Study equation [11–14]. However, to our knowledge, those new equations and novel filtration markers have not been assessed in relation to the risk of incident PAD.

Moreover, patients with CKD are prone to have abnormal bone-mineral metabolism (BMM), with altered serum levels of fibroblast growth factor 23 (FGF-23), parathyroid hormone (PTH), calcium, and phosphorus [15, 16]. These BMM biomarkers are reported to partially explain excess cardiovascular risk among persons with CKD [17, 18], but have not been comprehensively evaluated in the context of PAD risk.

Therefore, we comprehensively assessed the association of future risk of clinical PAD with multiple measures of kidney function and BMM using data from a bi-racial community-based cohort, the Atherosclerosis Risk in Communities (ARIC) Study. Our key hypotheses were as follows: 1) cystatin C and B2M would be more strongly associated with PAD risk compared with creatinine-based eGFR; 2) BMM markers would attenuate the association between kidney function and PAD risk; 3) and BMM markers would be associated with future PAD risk beyond kidney function. The first hypothesis has an implication for effectively identifying persons at high risk of incident PAD whereas the last two hypotheses

have implications for pathophysiological pathways linking kidney function to PAD risk as well as a potential therapeutic target to reduce the risk of PAD.

2. Patients and methods

2.1 Study design and population

The ARIC Study is a prospective cohort of 15,792 individuals aged from 45 to 64 years at visit 1 (1987–1989) from four communities in the U.S. (Forsyth County, NC; Jackson, MS; suburban Minneapolis, MN; and Washington County, MD) [19]. We used visit 2 (1990–1992) as baseline in this study, when all measures of kidney function and BMM markers of interest were collected. Of the 14,348 participants at visit 2, we excluded participants with race other than black or white (n=42), missing data on any of the variables of interest (n=1,797), or with a clinical history of PAD at baseline determined by self-reported leg artery revascularization at visit 1 and any PAD-related hospitalizations prior to visit 2 (n=37), yielding a final sample of 12,472 participants. Written informed consent was obtained from all participants.

2.2 Measurements

Information on demographic, life-style, and medical characteristics of participants was collected at visit 2 using standardized questionnaires by a trained interviewer. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Sitting blood pressures were measured three times after a five-minute rest using a sphygmomanometer, and the mean of the last two was recorded. Diabetes was defined as fasting glucose level ⩾126 mg/dL (⩾7.0 mmol/L), non-fasting glucose level ⩾200 mg/dL (⩾11.1 mmol/L), self-reported physician diagnosis, or use of anti-diabetic medications. Prevalent coronary heart disease was defined as cases adjudicated by physician-panel between visits 1 and 2 in addition to self-reported clinical history and evidence of prior myocardial infarction by electrocardiogram obtained at visit 1. Prevalent stroke was similarly defined by self-reported history at visit 1 and any adjudicated cases between visits 1 and 2. Medications were determined via self-reported usage in the past two weeks. Plasma total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured using automated enzymatic procedures, and low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation [20].

2.3 Kidney filtration and bone-mineral metabolism markers

eGFR was calculated using the CKD-EPI (CKD Epidemiology Collaboration) [21, 22] equations based on demographical variables, age, gender, race, and either or both filtration markers, serum creatinine and cystatin C (i.e., eGFRcr, eGFRcys, and eGFRcr-cys, respectively) [23]. Serum creatinine was measured by a modified kinetic Jaffé method, and serum cystatin C and B2M were measured by a particle-enhanced immunonephelometric assay using a BNII nephelometer (Siemens Healthcare Diagnostics). The reliability coefficient was 0.95 for serum creatinine, 0.94 for cystatin C, and 0.98 for B2M [14].

FGF-23 was measured via a 2-site ELISA (FGF-23 ELISA Kit; Kainos Laboratories, Tokyo, Japan) in serum samples collected during visit 2, with coefficient of variation (CV) 16.6%

from split paired samples and 8.8% from internal laboratory quality control samples at 41.4 pg/mL [24]. PTH was measured using a sandwich immunoassay method on a Roche Elecsys 2010 Analyzer (Roche Diagnostics Corporation), with CV 9.7%. Serum calcium and phosphorus were measured using colorimetric methods on a Roche Modular P Chemistry Analyzer (Roche Diagnostics Corporation), with CV 2.4% and 3.0% for calcium and phosphorus, respectively [25].

2.4 Definition of peripheral artery disease (PAD)

Based on previous literature [10, 26], clinical PAD was identified according to hospitalizations with the following ICD-9 discharge codes: 440.20, 440.21, 440.22, 440.23, 440.24, 440.29, 440.3, 440.4, 38.18, 39.25, 39.29, 39.50 (detailed in Supplementary Table1). Of PAD cases, participants with 440.22, 440.23, 440.24 and those with any concurrent ICD-9 codes of ulcer (707.1), gangrene (785.4), and leg amputation (84.1×) were considered as critical limb ischemia (CLI), a severe form of PAD [27]. Participants free of incident PAD were followed until the date of death, date of last contact, or December 31, 2012, whichever came first.

2.5 Statistical analysis

We summarized participants' baseline characteristics by incident PAD status. Spearman rank correlation coefficients were calculated between kidney filtration markers and BMM markers.

For prospective analyses, we first characterized the continuous association between measures of eGFR and incident PAD using Poisson regression models. We modeled eGFR measures as linear splines with knots at 30, 45, 60, 75, 90 and 105 mL/min/1.73 m^2, adjusting for age, gender and race. Subsequently, we examined the impact of potential confounders (details described below) using Cox proportional hazards regression models across clinical categories of eGFR ⩾90, 60–89, 30–59, and <30 mL/min/1.73 m^2 [23] Then, for a fair comparison of each of the filtration markers, we investigated their quartiles (top quartile as reference for all three eGFRs, and the lowest quartile as reference for the rest of markers). BMM markers were similarly modeled as quartiles.

To evaluate the attenuation of the associations between filtration markers and PAD risk by accounting for BMM markers, we built two models: Model 1 adjusted for traditional confounders at baseline including age, gender, race and ARIC visit center, education level, BMI, smoking status, alcohol drinking status, LDL cholesterol level, HDL cholesterol level, systolic blood pressure, use of anti-hypertensive medications, use of cholesterol-lowering medications, diabetes mellitus, prevalent coronary heart disease and prevalent stroke; and Model 2 additionally adjusted for all four BMM markers.

For the analysis of BMM markers as key exposures, we built three models (denoted as Model I to III). Specifically, Model I adjusted for demographic confounders including age, gender, race and ARIC visit center, Model II additionally adjusted for traditional cardiovascular risk factors (education level, BMI, smoking and alcohol drinking status, LDL cholesterol level, HDL cholesterol level, systolic blood pressure, use of anti-hypertensive

medication, use of cholesterol-lowering medication, diabetes mellitus, prevalent coronary heart disease and prevalent stroke), and Model III further adjusted for eGFRcr-cys.

Finally, we conducted subgroup analyses by key demographic and clinical subgroups according to age (⩾65 *vs.* <65 years), gender, race (black *vs.* white), smoking status (current/former *vs.* never) and the presence/absence of diabetes mellitus, hypertension (defined as systolic blood pressure ⩾140 mmHg, diastolic blood pressure ⩾90 mmHg, or taking any anti-hypertensive medication), cardiovascular disease (prevalent coronary heart disease or stroke) at baseline. Potential effect measure modification was tested using likelihood ratio test by comparing models with and without interaction terms.

All analyses were performed using Stata, version 13.0 (StataCorp LP, College Station, TX), and statistical significance level for p was set at 0.05.

3. Results

3.1 Baseline characteristics

The average age of the participants was 56.9 years (SD 5.7 years), and 75.4% (n=9,405) were white. Compared with participants who did not develop incident PAD during the follow-up, those who developed PAD were more likely to be older, male, black, current smokers, have diabetes and history of stroke and coronary heart disease, higher BMI, systolic blood pressure, LDL cholesterol level and lower HDL cholesterol level, and take cholesterol-lowering medication and anti-hypertensive medication, while less likely to be highly educated or current drinkers (Table 1). As shown in Table 2, kidney filtration markers were moderately to highly correlated with each other (|r| ranged from 0.46 to 0.97) but were weakly correlated with BMM markers (|r| ranged from 0.01 to 0.25). Correlations among BMM markers were also weak (|r| ranged from 0.08 to 0.20).

3.2 Associations of eGFRs with incident PAD and CLI

Out of 12,472 participants free of PAD at baseline, 471 participants developed PAD (crude incidence rate: 2.06 cases/1,000 person-years) during a median follow-up of 21 years, and 171 participants were considered CLI (crude incidence rate: 0.74 cases/1,000 person-years). After adjusting for age, males had higher PAD incidence rate relative to females (incidence rate per 1,000 person-years: 2.51 in men and 1.55 in women at mean age (57 years), p<0.001). Fig. 1 shows the demographically-adjusted incidence rate of PAD according to eGFRs. Regardless of the equations used, the incidence rate of PAD increased steadily below eGFR 105 mL/min/1.73 m^2, with risk gradient of 6–8 fold between eGFR 15 and 105 mL/min/1.73 m^2. As seen in other cardiovascular outcomes [28], an increased incidence rate of PAD was also observed when eGFR was greater than 105 mL/min/1.73 m^2, when creatinine was used for estimating GFR (Fig. 1A and C). This pattern was not particularly evident for eGFRcys (Fig. 1B).

With clinical categories of eGFR, we confirmed that the dose-response associations of eGFR categories with PAD risk even after accounting for other traditional cardiovascular risk factors (Model 1 in Table 3; [number of events and participants in each eGFR category were shown in Supplementary Table 2]). For all eGFR equations, participants with eGFRs <30

mL/min/1.73 m^2 had hazard ratio (HR) >10 compared to those in the reference group with eGFR ⩾90 mL/min/1.73 m^2. eGFR 30–59 mL/min/1.73 m^2 contributed to 2.4–3.5 fold higher risk compared to the reference group. Of note, even those with mildly reduced eGFR 60–89 mL/min/1.73 m^2 demonstrated significantly higher risk of PAD (1.3–1.5 fold) compared to the reference, when cystatin C was taken into account. The HR of PAD in each eGFR category were highest for eGFRcr-cys. When we adjusted for all four BMM markers, HR was evidently attenuated only in the category of eGFR<30 mL/min/1.73 m^2 (Model 2 in Table 3), but the associations still remained significant. The attenuation was mainly driven by PTH and phosphorus (Supplementary Table 3). We observed similar associations when CLI was investigated as the outcome of interest (Table 3).

According to the association between eGFRs and incident PAD observed in Figure 1 and Table 3, to obtain reliable estimates in every subgroup, we assessed whether the HR of PAD for every 15-unit lower eGFR below 105 mL/min/1.73 m^2 would differ in subgroups by age, gender, race, smoking status, hypertension, diabetes and prevalent cardiovascular disease status while adjusting for traditional cardiovascular risk factors plus BMM markers (i.e., Model 2) (Supplementary Table 4). We found low eGFR associated with incident PAD in all subgroups, and there were significant interactions by smoking status and diabetes, but importantly lower eGFR was positively associated with PAD risk in both strata of these subgroups.

3.3 Associations of novel filtration markers with incident PAD and CLI

When we contrasted three eGFRs, cystatin C, and B2M using their quartiles (Table 4), overall, B2M appeared to be most strongly and consistently associated with future PAD risk, with 2.6–2.7 fold higher risk between Q4 *vs.* Q1. Q3 showed significant results only for B2M, and even its Q2 reached significance for CLI. As the PAD risk was lowest in Q2 for eGFRs in several models, we also compared the associations with Q2 as reference and confirmed the highest HRs of PAD for Q4 of B2M (Supplementary Table 5). We confirmed similar associations for quartiles of cystatin C and B2M across the subgroups tested (Supplementary Table 6).

3.4 Associations of BMM markers with incident PAD and CLI

Neither PTH nor calcium demonstrated significant associations with PAD risk in all Models I to III with Q1 as reference (Table 5). FGF23 was positively associated with incident PAD when adjusted for traditional cardiovascular confounders (Q4 *vs.* Q1 HR=1.35 [95% CI: 1.05–1.75] in Model II); however, the association was no longer significant after further adjusting for eGFRcr-cys (Model III). Phosphorus was the only BMM marker showing significantly positive association with incident PAD, independently of traditional cardiovascular risk factors as well as kidney function. The HR of incident PAD comparing Q4 to Q1 for phosphorus was 1.56 [1.18–2.06] in Model II, and 1.47 [1.11–1.94] in Model III. Similar patterns were observed for CLI as the outcome.

4. Discussion

In this large community-based cohort study, we observed that reduced eGFR, regardless of the equation used, was associated with increased risk of future PAD in general population, independently of traditional cardiovascular risk factors. Participants with baseline eGFR <30 mL/min/1.73 m^2 had a greater than 10-fold higher risk of PAD compared to those with eGFR ⩾90 mL/min/1.73 m^2. eGFR 30–59 and 60–89 conferred a ~3-fold and a ~1.5-fold higher risk of future PAD, respectively. Of note, the associations tended to be more pronounced when kidney function was assessed with cystatin C and B2M as compared to the more conventional eGFRcr. The observed associations were generally consistent across various demographic and clinical subgroups. Adjustment for BMM markers attenuated the associations between kidney function and PAD risk solely when eGFR was below 30 mL/min/1.73 m^2. Of BMM markers, phosphorus was the only marker showing significant and consistent associations with PAD after accounting for traditional cardiovascular risk factors and kidney function. Based on a large sample size and long follow-up time, we confirmed similar patterns for CLI, a more severe form of PAD.

Several studies have reported the association between kidney function and PAD [8–10, 29–31]. However, ours is one of a few studies exploring this association in a prospective design [8–10]. Using various validated equations for eGFR and based on an adequate number of PAD cases over long follow-up, we were able to quantify the associations across clinical categories of eGFR. Further, the analyses specific to CLI are unique. Taken altogether, our results clearly support the important contributions of reduced kidney function to the pathophysiology of PAD development. FGF23, PTH, and phosphorus are considered as potential mechanisms linking CKD to systemic atherosclerosis [32–35], and our results suggest these BMM markers may partially explain this association between CKD and PAD risk when kidney function is severely reduced. Other suggested mechanisms linking CKD to atherosclerotic disease include inflammation, coagulation system activation, altered homocysteine metabolism, and oxidative stress [36–39].

Similar to other subtypes of cardiovascular outcomes, we observed that cystatin C and B2M are more strongly associated with PAD compared to creatinine-based eGFR [14]. As discussed previously, there may be kidney-related and non-kidney elements behind this observation [40]. Specifically, cystatin C and B2M may be superior to serum creatinine as filtration markers and indeed are less affected by diet and muscle mass. In terms of non-kidney elements, cystatin C and B2M are known to be linked to inflammation, which may contribute to their strong associations with atherosclerotic disease. In addition, B2M may also be indicative of amyloid deposition and aggregation in the vessel wall during the development of atherosclerosis [41, 42]. Of note, in a proteomic profiling study, out of ~1,600 protein peaks assessed, B2M was found to be most robustly associated with PAD [43].

We did not observe consistent associations of multiple BMM markers with PAD risk. The results for PTH are not necessarily surprising as it was not strongly associated with several cardiovascular diseases in a previous report from the ARIC Study [25]. FGF-23 has been shown to be associated with other subtypes of cardiovascular disease in some studies [44,

45], but its association with PAD in our study was no longer significant after adjusting for kidney function, which is consistent with prior data [46]. Of those BMM markers, phosphorus was the only one significantly associated with incident PAD even after accounting for kidney function. We extended similar observation in a cross-sectional study [47] to a prospective setting. Although the mechanisms behind this positive association is unclear, our findings are in line with a previous study showing the relationship for phosphorus with the risk of composite cardiovascular outcomes including coronary heart disease, stroke, PAD, and heart failure [35]. Unfortunately, this previous study did not report the specific results for incident PAD. Serum phosphorus is known to induce vascular calcification through mineralization of the extracellular matrix [48]. High phosphorus levels would also inhibit 1,25- dihydroxy vitamin D synthesis [33, 49], which might subsequently increase vascular calcification. Nonetheless, future investigations of the mechanisms linking phosphorus to the development of PAD are warranted.

Our study results may have some clinical and public health implications. These results highlight reduced kidney function, even at mild to moderate stage, is a risk factor for PAD and CLI, independently of well-known traditional cardiovascular risk factors. Especially, cystatin C and B2M may lead to better risk stratification of future PAD. Given a possible role for phosphorus in the pathophysiology of PAD suggested in our study, future investigations would be warranted regarding whether controlling serum phosphorus levels could reduce PAD risk. This may be important since there are no established treatments to recover kidney function, but phosphate-binding agents are clinically available for patients with CKD. In this context, it may be worth recognizing that a high phosphorus diet may raise serum phosphorus levels [50].

Admittedly, this study had several limitations. First, identifying PAD and CLI cases based on ICD-9 codes from hospitalization records limited the sensitivity in outcome ascertainment, though this method is likely to be specific and capture severe symptomatic patients requiring hospitalizations. Secondly, we were not able to take into account albuminuria, the other key measure of CKD, since it was not measured at visit 2. Thirdly, kidney function and BMM markers as well as other covariates were measured only once at baseline, which may lead to potential misclassification. However, this type of misclassification usually results in more conservative estimates. Finally, we cannot rule out the possibility of residual confounding, as true in any observational study.

In summary, reduced kidney function, even at mild to moderate stages, was independently associated with future PAD risk. The associations were particularly evident when kidney function was evaluated by cystatin C or B2M. Although overall the associations between BMM markers and PAD risk were not consistent, serum phosphorus demonstrated a robust association. These findings confirm the importance of PAD as a complication in persons with reduced kidney function. Also, our findings suggest the usefulness of cystatin C and B2M for assessing PAD risk and a potential role of phosphorus in the pathophysiology of PAD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Even mild to moderate kidney dysfunction was independently associated with incident PAD.
- The association was particularly evident when kidney function was assessed with cystatin C or B2M.
- Among BMM markers tested, phosphorus was most robustly associated with incident PAD.

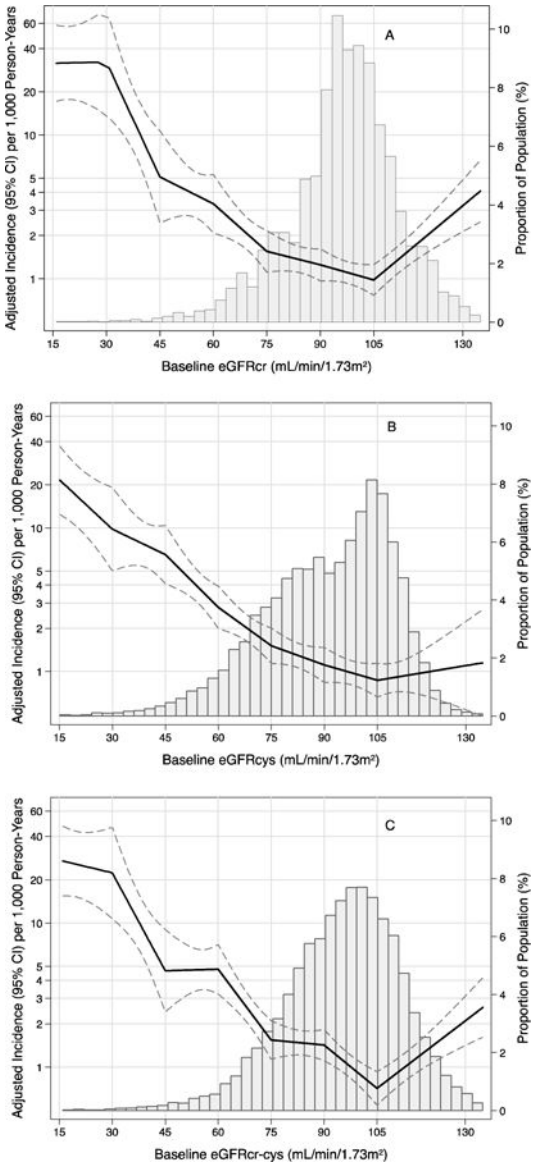

Figure 1.

Age-, gender-, and race-adjusted incident rate of PAD according to baseline eGFRs using different equations (with knots at 30, 45, 60, 75, 90 and 105 mL/min/1.73m^2).

(A) eGFRcr; (B) eGFRcys; (C) eGFRcr-cys.

Table 1

Baseline characteristics of participants by incident PAD status in the ARIC Study 1990–2012.

Variables	Total	Incident PAD		*p*-value
	(n=12472)	Yes (n=471)	No (n=12001)	
Age (years)	56.9 ± 5.7	58.8 ± 5.6	56.8 ± 5.7	<0.001
Male	5431 (43.6)	258 (54.8)	5173 (43.1)	<0.001
Black	3067 (24.6)	142 (30.1)	2925 (24.4)	0.004
Education [a]				
Basic	2631 (21.1)	159 (33.8)	2472 (20.6)	<0.001
Intermediate	5208 (41.8)	177 (37.6)	5031 (41.9)	
Advanced	4633 (37.2)	135 (28.7)	4498 (37.5)	
Body mass index (kg/m^2)	28.0 ± 5.4	29.0 ± 5.8	27.9 ± 5.4	<0.001
Mean systolic blood pressure (mmHg)	121.2 ± 18.6	128.8 ± 20.9	120.9 ± 18.4	<0.001
Mean diastolic blood pressure (mmHg)	72.1 ± 10.2	72.0 ± 11.2	72.1 ± 10.2	0.928
Use of anti-hypertensive medication	4015 (32.2)	259 (55.0)	3756 (31.3)	<0.001
LDL cholesterol (mg/dL)	133.4 ± 36.7	142.7 ± 40.2	133.1 ± 36.6	<0.001
HDL cholesterol (mg/dL)	50.1 ± 16.7	42.9 ± 13.5	50.3 ± 16.7	<0.001
Use of cholesterol-lowering medication	783 (6.3)	56 (11.9)	727 (6.1)	<0.001
Smoking				<0.001
Current	2726 (21.9)	177 (37.6)	2549 (21.2)	
Former	4719 (37.8)	174 (36.9)	4545 (37.9)	
Never	5027 (40.3)	120 (25.5)	4907 (40.9)	
Alcohol drinking				0.007
Current	7073 (56.7)	250 (53.1)	6823 (56.9)	
Former	2588 (20.8)	125 (26.5)	2463 (20.5)	
Never	2811 (22.5)	96 (20.4)	2715 (22.6)	
Prevalent coronary heart disease	693 (5.6)	92 (19.5)	601 (5.0)	<0.001
Prevalent stroke	236 (1.9)	23 (4.9)	213 (1.8)	<0.001
Prevalent diabetes	1779 (14.3)	184 (39.1)	1595 (13.3)	<0.001
eGFRcr (mL/min/1.73 m^2)	96.4 ± 15.6	90.8 ± 22.8	96.6 ± 15.2	<0.001
eGFRcys (mL/min/1.73 m^2)	90.9 ± 18.3	80.8 ± 23.6	91.3 ± 17.9	<0.001
eGFRcr-cys (mL/min/1.73 m^2)	95.2 ± 17.0	86.7 ± 23.7	95.6 ± 16.6	<0.001
Cystatin C (mg/L)	0.9 [0.8–1.0]	0.9 [0.8–1.1]	0.9 [0.8–1.0]	<0.001
B2M (mg/L)	1.8 [1.6–2.1]	2.0 [1.8–2.4]	1.8 [1.6–2.1]	<0.001
FGF23 (pg/mL)	41.8 [33.9–51.6]	44.7 [35.5–57.0]	41.7 [33.8–51.4]	<0.001
PTH (pg/mL)	39.4 [31.2–49.5]	39.7 [29.9–49.6]	39.3 [31.2–49.5]	0.525
Calcium (mg/dL)	9.3 ± 0.4	9.4 ± 0.4	9.3 ± 0.4	0.069
Phosphorus (mg/dL)	3.5 ± 0.5	3.6 ± 0.6	3.5 ± 0.5	0.011

Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation or median [25th percentile–75th percentile].

[a]No or basic, less than high school; intermediate, high school graduate or vocational school; advanced, college, graduate school, or professional school.

Table 2

Spearman rank correlation coefficients between filtration markers and BMM markers at baseline.

	eGFRcr	eGFRcys	eGFRcr-cys	cystatin C	B2M	FGF23	PTH	Ca	P
eGFRcr	1.000								
eGFRcys	0.519	1.000							
eGFRcr-cys	0.809	0.905	1.000						
cystatin C	−0.516	−0.968	−0.898	1.000					
B2M	−0.458	−0.773	−0.728	0.762	1.000				
FGF23	−0.165	−0.244	−0.238	0.249	0.237	1.000			
PTH	−0.003	−0.023	−0.008	−0.004	0.015	0.080	1.000		
Ca	−0.048	−0.124	−0.101	0.111	0.095	0.129	−0.091	1.000	
P	0.077	−0.042	0.018	−0.021	0.017	0.110	−0.135	0.201	1.000

B2M, beta-2 microglobulin; FGF23, fibroblast growth factor 23; PTH, parathyroid hormone; Ca, calcium; P, phosphorus.

Table 3

Hazard ratios (95% confidence intervals) for incident PAD, CLI according to clinical cutoffs of baseline eGFR using different markers-ARIC Study 1990–2012.

Markers	CKD stage eGFR clinical cutoffs (mL/min/1.73 m^2)			
	>=90	60–89	30–59	<30
PAD (471 events/12,472 participants)				
Model 1				
eGFRcr	1.00 (ref)	1.20 (0.97,1.48)	2.88[c] (1.87,4.42)	12.76[c] (6.58,24.74)
eGFRcys	1.00 (ref)	1.26[a] (1.01,1.55)	2.38[c] (1.73,3.26)	11.62[c] (6.67,20.25)
eGFRcr-cys	1.00 (ref)	1.47[c] (1.19,1.81)	3.46[c] (2.41,4.96)	14.09[c] (7.66,25.92)
Model 2				
eGFRcr	1.00 (ref)	1.21 (0.98,1.50)	2.79[c] (1.81,4.30)	6.30[c] (2.47,16.03)
eGFRcys	1.00 (ref)	1.26[a] (1.01,1.56)	2.37[c] (1.73,3.25)	7.49[c] (3.81,14.71)
eGFRcr-cys	1.00 (ref)	1.47[c] (1.19,1.81)	3.45[c] (2.40,4.96)	8.33[c] (3.72,18.65)
CLI (171 events/12,472 participants)				
Model 1				
eGFRcr	1.00 (ref)	0.78 (0.53,1.14)	2.51[b] (1.30,4.83)	15.44[c] (6.79,35.11)
eGFRcys	1.00 (ref)	1.03 (0.72,1.48)	2.22[b] (1.34,3.66)	14.25[c] (6.71,30.27)
eGFRcr-cys	1.00 (ref)	1.13 (0.79,1.62)	2.89[c] (1.61,5.18)	14.64[c] (6.42,33.37)
Model 2				
eGFRcr	1.00 (ref)	0.79 (0.54,1.15)	2.41[b] (1.24,4.65)	4.60[c] (1.32,16.00)
eGFRcys	1.00 (ref)	1.02 (0.71,1.47)	2.18[b] (1.32,3.60)	6.02[c] (2.22,16.36)
eGFRcr-cys	1.00 (ref)	1.14 (0.79,1.63)	2.77[b] (1.54,4.99)	4.43[a] (1.31,15.00)

[a] $p<0.05$,

[b] $p<0.01$,

[c] $p<0.001$.

Model 1 adjusted for age, gender, race, ARIC visit center, education level, BMI, smoking status, alcohol drinking status, LDL level, HDL level, systolic blood pressure, anti-hypertensive medication, lowering-cholesterol medication, diabetes, prevalent coronary heart disease and prevalent stroke.

Model 2 adjusted for covariates in Model 1 plus FGF23, PTH, calcium and phosphorus.

Table 4

Hazard ratios (95% confidence intervals) for incident PAD and CLI according to quartiles of kidney function markers (Q1 indicates better kidney function) with and without adjustment for bone mineral metabolism markers in the ARIC Study 1990–2012.

Markers	Q1	Q2	Q3	Q4
PAD				
Model 1				
eGFRcr	1.00 (ref)	0.69[a] (0.50,0.95)	0.90 (0.67,1.22)	1.22 (0.93,1.62)
eGFRcys	1.00 (ref)	0.97 (0.70,1.34)	1.06 (0.77,1.44)	1.71[b] (1.26,2.31)
eGFRcr-cys	1.00 (ref)	0.83 (0.61,1.14)	0.99 (0.73,1.33)	1.49[b] (1.11,2.00)
cystatin C	1.00 (ref)	1.25 (0.91,1.72)	1.03 (0.74,1.44)	1.95[c] (1.44,2.65)
B2M	1.00 (ref)	1.24 (0.89,1.73)	1.68[b] (1.22,2.31)	2.69[c] (1.98,3.65)
Model 2				
eGFRcr	1.00 (ref)	0.68 (0.50,0.93)	0.88 (0.65,1.20)	1.20 (0.91,1.58)
eGFRcys	1.00 (ref)	0.96 (0.70,1.33)	1.06 (0.78,1.45)	1.65[b] (1.21,2.23)
eGFRcr-cys	1.00 (ref)	0.81 (0.59,1.11)	0.98 (0.72,1.33)	1.43[a] (1.07,1.92)
cystatin C	1.00 (ref)	1.25 (0.91,1.71)	1.04 (0.75,1.46)	1.91[c] (1.40,2.60)
B2M	1.00 (ref)	1.24 (0.89,1.73)	1.69[b] (1.23,2.32)	2.60[c] (1.91,3.54)
CLI				
Model 1				
eGFRcr	1.00 (ref)	0.56[a] (0.33,0.96)	1.04 (0.65,1.68)	0.93 (0.60,1.45)
eGFRcys	1.00 (ref)	0.98 (0.59,1.65)	1.12 (0.68,1.84)	1.35 (0.82,2.22)
eGFRcr-cys	1.00 (ref)	1.01 (0.62,1.65)	0.99 (0.61,1.61)	1.31 (0.82,2.10)
cystatin C	1.00 (ref)	1.36 (0.83,2.22)	1.11 (0.66,1.87)	1.58 (0.97,2.58)
B2M	1.00 (ref)	1.72[a] (1.00,2.95)	2.18[b] (1.29,3.69)	2.60[c] (1.54,4.38)
Model 2				
eGFRcr	1.00 (ref)	0.55[a] (0.32,0.95)	1.01 (0.63,1.63)	0.86 (0.56,1.34)
eGFRcys	1.00 (ref)	0.98 (0.58,1.65)	1.14 (0.69,1.87)	1.25 (0.76,2.05)
eGFRcr-cys	1.00 (ref)	0.98 (0.60,1.59)	0.98 (0.60,1.60)	1.19 (0.74,1.92)
cystatin C	1.00 (ref)	1.38 (0.84,2.25)	1.14 (0.68,1.92)	1.48 (0.90,2.44)
B2M	1.00 (ref)	1.73[a] (1.01,2.98)	2.19[b] (1.29,3.71)	2.39[b] (1.41,4.05)

[a] $p<0.05$

[b] $p<0.01$

[c] $p<0.001$.

Model 1 adjusted for age, gender, race, ARIC visit center, education level, BMI, smoking status, alcohol drinking status, LDL level, HDL level, systolic blood pressure, anti-hypertensive medication, lowering-cholesterol medication, diabetes, prevalent coronary heart disease and prevalent stroke.

Model 2 adjusted for covariates in Model 1 plus FGF23, PTH, calcium and phosphorus.

Quartiles for kidney function markers:

eGFRcr (mL/min/1.73 m^2): Q1: ≥ 105.64, Q2: 97.44–<105.64, Q3: 88.68–< 97.44, Q4: < 88.68.

eGFRcys (mL/min/1.73 m^2): Q1: ≥ 104.85, Q2: 93.74–<104.85, Q3: 79.02–< 93.74, Q4: < 79.02.

eGFRcr-cys (mL/min/1.73 m^2): Q1: Q1: ≥106.63, Q2: 96.69–<106.63, Q3: 85.17–< 96.69, Q4: < 85.17.

cystatin C (mg/L): Q1: <0.76, Q2: 0.76–< 0.86, Q3: 0.86–< 0.97, Q4: ≥0.97.

B2M (mg/L): Q1: <1.62, Q2: 1.62–< 1.84, Q3: 1.84–< 2.11, Q4: ≥2.11.

Table 5

Hazard ratios (95% confidence intervals) for incident PAD and CLI according to quartiles of bone-mineral metabolism markers (1st quartile as referent) in the ARIC Study 1990–2012.

Markers	Q1	Q2	Q3	Q4
PAD				
Model I				
FGF23	1.00 (ref)	0.95 (0.72,1.25)	1.09 (0.83,1.42)	1.58[c] (1.23,2.02)
PTH	1.00 (ref)	0.64[b] (0.49,0.83)	0.86 (0.67,1.10)	0.80 (0.62,1.03)
Calcium	1.00 (ref)	1.06 (0.81,1.39)	1.16 (0.91,1.48)	1.21 (0.94,1.57)
Phosphorus	1.00 (ref)	1.09 (0.84,1.40)	1.09 (0.85,1.41)	1.62[b] (1.23,2.13)
Model II				
FGF23	1.00 (ref)	0.95 (0.72,1.26)	1.01 (0.77,1.32)	1.35[a] (1.05,1.75)
PTH	1.00 (ref)	0.72[a] (0.55,0.94)	0.91 (0.71,1.16)	0.86 (0.66,1.12)
Calcium	1.00 (ref)	0.98 (0.74,1.28)	1.04 (0.82,1.33)	0.95 (0.73,1.24)
Phosphorus	1.00 (ref)	1.19 (0.92,1.53)	1.12 (0.87,1.44)	1.56[b] (1.18,2.06)
Model III				
FGF23	1.00 (ref)	0.92 (0.70,1.22)	0.96 (0.73,1.25)	1.12 (0.86,1.46)
PTH	1.00 (ref)	0.70[b] (0.54,0.92)	0.92 (0.72,1.18)	0.80 (0.61,1.04)
Calcium	1.00 (ref)	0.98 (0.74,1.28)	1.01 (0.79,1.29)	0.87 (0.67,1.14)
Phosphorus	1.00 (ref)	1.18 (0.91,1.52)	1.12 (0.87,1.45)	1.47[b] (1.11,1.94)
CLI				
Model I				
FGF23	1.00 (ref)	0.70 (0.44,1.12)	0.95 (0.62,1.46)	1.31 (0.88,1.95)
PTH	1.00 (ref)	0.78 (0.51,1.21)	0.91 (0.60,1.37)	0.68 (0.44,1.05)
Calcium	1.00 (ref)	1.07 (0.67,1.68)	1.00 (0.66,1.52)	1.28 (0.85,1.94)
Phosphorus	1.00 (ref)	1.06 (0.69,1.63)	1.01 (0.66,1.54)	1.51 (0.97,2.36)
Model II				
FGF23	1.00 (ref)	0.67 (0.42,1.07)	0.84 (0.55,1.30)	1.02 (0.68,1.53)
PTH	1.00 (ref)	0.82 (0.53,1.27)	0.87 (0.57,1.32)	0.66 (0.42,1.03)
Calcium	1.00 (ref)	0.93 (0.59,1.48)	0.90 (0.59,1.38)	0.97 (0.63,1.48)
Phosphorus	1.00 (ref)	1.24 (0.80,1.92)	1.14 (0.74,1.74)	1.66[a] (1.05,2.62)
Model III				
FGF23	1.00 (ref)	0.65 (0.41,1.05)	0.81 (0.53,1.26)	0.87 (0.57,1.32)
PTH	1.00 (ref)	0.79 (0.51,1.23)	0.88 (0.58,1.34)	0.60[a] (0.39,0.95)
Calcium	1.00 (ref)	0.95 (0.60,1.51)	0.89 (0.59,1.36)	0.93 (0.61,1.42)
Phosphorus	1.00 (ref)	1.23 (0.80,1.91)	1.16 (0.76,1.78)	1.59[a] (1.01,2.51)

[a] $p<0.05$,

[b] $p<0.01$,

[c] $p<0.001$.

Model I adjusted for age, gender, race and ARIC visit center.

Model II adjusted for covariates in Model I plus education level, BMI, smoking status, alcohol drinking status, LDL level, HDL level, systolic blood pressure, anti-hypertensive medication, lowering-cholesterol medication, diabetes, prevalent coronary heart disease and prevalent stroke.

Model III adjusted for covariates in Model II plus eGFRcr-cys.

Quartiles for BMM markers:

FGF23 (pg/mL): Q1: <33.88, Q2: 33.88–<41.78, Q3: 41.78–< 51.56, Q4: ≥ 51.56.

PTH (pg/mL): Q1: <31.19, Q2: 31.19–<39.38, Q3: 39.38–< 49.46, Q4: ≥49.46.

Calcium (mg/dL): Q1: <9.2, Q2: 9.2–<9.4, Q3: 9.4–< 9.7, Q4: ≥9.7.

Phosphorus (mg/dL): Q1: <3.3, Q2: 3.3–< 3.6, Q3: 3.6–< 4.0, Q4: ≥4.0.