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Coronary Artery Calcification and Risk of Cardiovascular Disease and Death Among Patients With Chronic Kidney Disease

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IMPORTANCE Coronary artery calcification (CAC) is highly prevalent in dialysis-naive patients with chronic kidney disease (CKD). However, there are sparse data on the association of CAC with subsequent risk of cardiovascular disease and all-cause mortality in this population.

OBJECTIVE To study the prospective association of CAC with risk of cardiovascular disease and all-cause mortality among dialysis-naive patients with CKD.

DESIGN, SETTING, AND PARTICIPANTS The prospective Chronic Renal Insufficiency Cohort study recruited adults with an estimated glomerular filtration rate of 20 to 70 mL/min/1.73 m^2 from 7 clinical centers in the United States. There were 1541 participants without cardiovascular disease at baseline who had CAC scores.

EXPOSURES Coronary artery calcification was assessed using electron-beam or multidetector computed tomography.

MAIN OUTCOMES AND MEASURES Incidence of cardiovascular disease (including myocardial infarction, heart failure, and stroke) and all-cause mortality were reported every 6 months and confirmed by medical record adjudication.

RESULTS During an average follow-up of 5.9 years in 1541 participants aged 21 to 74 years, there were 188 cardiovascular disease events (60 cases of myocardial infarction, 120 heart failures, and 27 strokes; patients may have had >1 event) and 137 all-cause deaths. In Cox proportional hazards models adjusted for age, sex, race, clinical site, education level, physical activity, total cholesterol level, high-density lipoprotein cholesterol level, systolic blood pressure, use of antihypertensive treatment, current cigarette smoking, diabetes status, body mass index, C-reactive protein level, hemoglobin A_{1c} level, phosphorus level, troponin T level, log N-terminal pro–B-type natriuretic peptide level, fibroblast growth factor 23 level, estimated glomerular filtration rate, and proteinuria, the hazard ratios associated with per 1 SD log of CAC were 1.40 (95% CI, 1.16-1.69; $P < .001$) for cardiovascular disease, 1.44 (95% CI, 1.02-2.02; $P = .04$) for myocardial infarction, 1.39 (95% CI, 1.10-1.76; $P = .006$) for heart failure, and 1.19 (95% CI, 0.94-1.51; $P = .15$) for all-cause mortality. In addition, inclusion of CAC score led to an increase in the C statistic of 0.02 (95% CI, 0-0.09; $P < .001$) for predicting cardiovascular disease over use of all the above-mentioned established and novel cardiovascular disease risk factors.

CONCLUSIONS AND RELEVANCE Coronary artery calcification is independently and significantly related to the risks of cardiovascular disease, myocardial infarction, and heart failure in patients with CKD. In addition, CAC improves risk prediction for cardiovascular disease, myocardial infarction, and heart failure over use of established and novel cardiovascular disease risk factors among patients with CKD; however, the changes in the C statistic are small.

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Supplemental content

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Cardiovascular disease is the major cause of premature death in patients with chronic kidney disease (CKD).[1,2] Large prospective cohort studies have documented significant associations of worse kidney function and proteinuria with cardiovascular disease and mortality that are independent of traditional risk factors.[2-4] Coronary artery calcification (CAC) is highly prevalent and more severe in patients with CKD compared with those without CKD.[5-7] Coronary artery calcification independently predicts the risk of coronary heart disease and total cardiovascular disease more than traditional risk factors in the general population.[8,9]

However, there are sparse data available from dialysis-naive patients with CKD and it is uncertain whether CAC score confers an elevated risk of cardiovascular disease morbidity and mortality in such patients.[10] In a subgroup analysis of 1284 participants with CKD from the Multi-Ethnic Study of Atherosclerosis, CAC score, carotid intima-media thickness, and ankle-brachial index improved cardiovascular disease risk prediction, and the greatest improvement in risk prediction was observed with CAC score.[11] However, the following cardiovascular disease risk factors that are especially important for patients with CKD were not adjusted for in that analysis[11]: inflammatory biomarkers, hemoglobin A_{1c} level, phosphorus level, N-terminal pro-B-type natriuretic peptide (NT-proBNP) level, fibroblast growth factor 23 level, kidney function, and proteinuria.

The objectives of the Chronic Renal Insufficiency Cohort (CRIC) study were to investigate the prospective association of CAC with risk of cardiovascular disease and all-cause mortality in dialysis-naive patients with CKD after adjusting for important risk factors for cardiovascular disease, and to assess whether inclusion of CAC improves cardiovascular disease risk prediction over use of the American College of Cardiology (ACC) and the American Heart Association (AHA) atherosclerotic cardiovascular disease risk factors and other novel risk factors.[12]

Key Points

Question Does coronary artery calcification (CAC) predict cardiovascular disease risk among patients with chronic kidney disease (CKD)?

Findings In this prospective cohort study, 1 SD log higher in CAC score was significantly associated with a 40% higher risk of cardiovascular disease, a 44% higher risk of myocardial infarction, and a 39% higher risk of heart failure after adjusting for important risk factors. Inclusion of CAC score led to a significant increase in the C statistic for predicting cardiovascular disease over use of established and novel risk factors among patients with CKD.

Meaning Use of the CAC score improves risk prediction for cardiovascular disease, myocardial infarction, and heart failure over use of established and novel risk factors among patients with CKD.

Methods

Study Participants

The CRIC study included a racially and ethnically diverse group of men and women aged 21 to 74 years with mild to moderate CKD (age-based estimated glomerular filtration rate [eGFR] entry criteria of 20-70 mL/min/1.73 m^2). A total of 3939 patients were recruited between May 2003 and August 2008 from 7 clinical centers in the United States.[13] Patients were identified through searches of laboratory databases, medical records, and referrals from health care providers. Patients with cirrhosis, human immunodeficiency virus infection, polycystic kidney disease, or renal cell carcinoma; those receiving dialysis or recipients of a kidney transplant; or those taking immunosuppressant drugs were excluded. In addition, patients with a history of coronary artery revascularization were excluded from electron-beam or multidetector computed tomography (CT). Of these CRIC study participants, 1142 patients were randomly selected from all study sites and stratified by age, sex, race/ethnicity, diabetes status, and eGFR level for electron-beam or multidetector CT without any oversampling.

In addition, electron-beam or multidetector CT was performed in all eligible participants from 3 clinical centers for an ancillary study. Data on CAC were available for a total of 2069 patients.[5] Of the 2069 patients, there were 528 who reported a history of coronary artery disease, heart failure, atrial fibrillation, stroke, or peripheral vascular disease at baseline and were excluded, leaving 1541 for this analysis.

The CRIC study was approved by the institutional review boards from each participating institution. Written informed consent was obtained from all participants. The CRIC study also conformed to the Health Insurance Portability and Accountability Act guidelines.

Baseline Measurement

All CRIC study data were collected by trained study staff during the baseline and annual clinical visits. All data collection procedures and equipment were standardized across the 7 study sites. Baseline information on demographic characteristics, lifestyle risk factors, history of cardiovascular disease, and use of medications was obtained by standard questionnaire. Race/ethnicity was self-reported and used as a covariable in the analysis. Cigarette smoking was defined by lifetime smoking of more than 100 cigarettes and alcohol consumption as drinking 1 or more alcoholic beverages each week during the previous year.

Physical activity was calculated as total metabolic equivalents per week. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared and was used as an index for obesity. Three seated blood pressure measurements using an aneroid sphygmomanometer after at least 5 minutes of quiet rest were obtained by trained and certified staff who followed a standard protocol, with the averages of 3 measurements used for the analysis.[14] Hypertension was defined as a systolic blood pressure of 140 mm Hg or greater, a diastolic blood pressure of 90 mm Hg or greater, or current use of an antihypertensive medication.

Levels of glucose, cholesterol, triglycerides, glycated hemoglobin A_{1c}, phosphorus, calcium, total parathyroid hormone, and alkaline phosphatase were measured using standard laboratory methods. Levels of high-sensitivity

C-reactive protein (CRP) and cystatin C were measured using the particle-enhanced immunonephelometry method. High-sensitivity troponin T level was measured using the Roche Elecsys immunoassay (Roche Diagnostics). N-terminal pro-B-type natriuretic peptide level was measured using the Elecsys 2010 analyzer (Roche Diagnostics). Fibroblast growth factor 23 level was measured using a second-generation C-terminal assay (Immutopics). Creatinine level was measured using an enzymatic method on an Ortho Vitros 950 and standardized to isotope-dilution mass spectrometry traceable values. Estimated glomerular filtration rate was calculated using the estimated equation derived from the CRIC cohort.[15]

Diabetes was defined as a fasting plasma glucose level of 126 mg/dL or greater (to convert glucose to mmol/L, multiply by 0.0555), a nonfasting plasma glucose level of 200 mg/dL or greater, or self-reported use of any antidiabetes medication. A 24-hour urine specimen was collected and urinary protein concentration was determined using the turbidometric method with benzethonium chloride. All laboratory measurements were conducted at the CRIC study central laboratory at the University of Pennsylvania with stringent quality control.

As a part of the CRIC protocol, a subcohort of participants underwent CAC measurement with either electron-beam or multidetector CT at 1 year. Trained and certified technologists scanned all participants twice using phantoms of known physical calcium concentrations. A cardiologist read all CT scans at a central reading center (Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center).

The total Agatston score, which is a pseudo-continuous variable derived from plaque densities and their areas in all coronary arteries, was computed.[16] The average Agatston score from the 2 scans was used in all the analyses. Based on the distribution of Agatston scores, the CRIC participants were divided into CAC score categories of 0 (no CAC), greater than 0 to 100 (moderate CAC), or greater than 100 (severe CAC). In addition, CAC per 1 SD log was calculated and used as a continuous variable for the analysis.

Assessment of Outcomes

Patients were followed up annually via clinic visits and interim telephone contact at 6 months. Cardiovascular disease (including myocardial infarction, heart failure, and stroke) outcomes were assessed using a standard Medical Event Questionnaire during all follow-up contacts. If patients were hospitalized or stayed overnight in an emergency department due to a cardiovascular disease event, including those who later died, their medical records were requested for cardiovascular event verification. Two physicians adjudicated each cardiovascular event, classifying each as either probable or definite.

Heart failure was identified by hospital admission for new or worsening heart failure signs and symptoms and diminished cardiac output. Myocardial infarction was defined by characteristic changes in levels of troponin T and creatine kinase myocardial band, symptoms of myocardial ischemia, changes in electrocardiogram results, new fixed-perfusion abnormalities, or a combination of these. Stroke was defined as rapid onset of a neurological deficit, headache, or other nonvascular cause, by presence of a clinically relevant lesion on brain imaging for longer than 24 hours, or death within 24 hours.

All events classified as probable or definite during adjudication were included in the analyses. Due to lack of cause-specific information regarding out-of-hospital deaths, these events were not included in the analysis. Follow-up was censored at the time of study outcome onset, death, withdrawal, loss to follow-up, or the end of the follow-up period, whichever occurred first.

Statistical Methods

Baseline characteristics of participants were summarized as mean (SD) for continuous variables, percentage for categorical variables, or median (interquartile range) for variables with skewed distribution by CAC categories. Statistical significance was tested using analysis of variance for continuous variables and χ^2 tests for categorical variables. Logarithmic transformations were performed for severely skewed variables to stabilize variances and normalize distributions.

Cumulative rates of cardiovascular disease (included myocardial infarction, heart failure, and stroke), myocardial infarction, heart failure, and all-cause mortality were calculated using the Kaplan-Meier method by CAC score categories and compared using the log-rank test with the null hypothesis that the cumulative incidence was the same across the CAC score categories.[17] Hazard ratios for the associations of CAC categories or log CAC scores with cardiovascular disease, myocardial infarction, heart failure, and death were estimated using Cox proportional hazards models with follow-up used as the time scale.[18] The assumption of proportionality was tested using Schoenfeld residuals and interaction terms with time for each exposure variable and covariate. No substantial deviations from proportionality were observed.

For each outcome and exposure (categorical and log CAC scores), 3 models were fitted. Model 1 adjusted for age, sex, race, and clinical sites; model 2 adjusted for the factors in model 1 and the ACC/AHA atherosclerotic cardiovascular disease risk factors (age, sex, race, clinical site, total cholesterol level, high-density lipoprotein cholesterol level, systolic blood pressure, use of antihypertensive treatment, current cigarette smoking, and diabetes status); and model 3 adjusted for factors in models 1 and 2 plus education level, BMI, physical activity, high-sensitivity CRP level, hemoglobin A_{1c} level, phosphorus level, high-sensitivity troponin T level, NT-proBNP level, fibroblast growth factor 23 level, eGFR, and 24-hour urinary protein level using backward elimination. Complete case analysis was used for the main findings. Multiple imputation for missing covariate values was performed in a sensitivity analysis, and no substantial differences were observed.

To assess the added value of CAC in prediction models, multivariable Cox proportional hazards models were compared with and without CAC score. The C statistic, the C statistic difference with or without CAC score, continuous net reclassification improvement, and integrated discrimination improvement were evaluated using methods accounting for censoring.[19,20] The C statistic measures concordance between model-based risk estimates and observed events (equivalent to the area under the receiver operating characteristic curve).

Figure 1. Chronic Renal Insufficiency Cohort Study Participants by Coronary Artery Calcification Score and Estimated Glomerular Filtration Rate

A score of 0 indicates no coronary artery calcification; greater than 0 to 100, moderate calcification; greater than 100, severe calcification.

The net reclassification improvement and integrated discrimination improvement are statistics proposed as measures of the incremental prognostic effect that a new biomarker will have when added to an existing prediction model. Net reclassification improvement is interpreted as the proportion of patients reclassified to a more appropriate risk category when a new biomarker is added to the prediction model. Integrated discrimination improvement is defined as an improvement in discrimination slopes (ie, the difference in means of model-based risks for events minus nonevents) if adding a new biomarker to the prediction model. Bootstrapping methods were used to obtain 95% CIs. All analyses were conducted using SAS version 9.1 (SAS Institute Inc). All *P* values were 2-sided and statistical significance was defined as $P < .05$.

Results

Among 1541 CRIC participants without a self-reported history of cardiovascular disease, 302 (19.6%) had an eGFR of less than 30 mL/min/1.73 m^2, 467 (30.3%) had an eGFR of 30 to 44 mL/min/1.73 m^2, 419 (27.2%) had an eGFR of 45 to 59 mL/min/1.73 m^2, and 353 (22.9%) had an eGFR of 60 mL/min/1.73 m^2 or greater (eFigure 1 in the Supplement). Of 451 participants who had a CAC score of greater than 100, 109 (24.2%) had an eGFR of less than 30 mL/min/1.73 m^2, 158 (35.0%) had an eGFR of 30 to 44 mL/min/1.73 m^2, 131 (29.0%) had an eGFR of 45 to 59 mL/min/1.73 m^2, and 53 (11.8%) had an eGFR of 60 mL/min/1.73 m^2 (**Figure 1**).

Baseline characteristics of participants according to CAC score categories appear in **Table 1**. Compared with those without CAC, participants with moderate or severe CAC were more likely to be older and male, less likely to be physically active, and more likely to have a history of hypertension and diabetes, and use of antihypertensive and lipid-lowering medications. On average, participants with CAC had higher levels of BMI, systolic blood pressure, hemoglobin A_{1c}, phosphorus, high-sensitivity troponin T, NT-proBNP, fibroblast growth factor 23, and urinary protein, but lower levels of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and eGFR.

During an average follow-up of 5.9 years, there were 188 cardiovascular disease events (60 cases of myocardial infarction, 120 heart failures, and 27 strokes; patients may have had >1 event) and 137 all-cause deaths. Kaplan-Meier cumulative incidence plots showed that moderate and severe CAC were associated with higher cumulative incidence of cardiovascular disease, myocardial infarction, heart failure, and all-cause mortality (**Figure 2**). After adjustment for age, sex, race, and clinic sites, moderate and severe CAC were significantly associated with higher risk of cardiovascular disease, myocardial infarction, heart failure, and all-cause mortality (**Table 2**). After additional adjustment for ACC/AHA atherosclerotic cardiovascular disease risk factors (total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, antihypertensive treatment, current cigarette smoking, and diabetes), the associations were slightly diminished but remained highly significant for severe CAC.

After further adjustment for important cardiovascular disease risk factors in patients with CKD, including education level, BMI, physical activity, high-sensitivity CRP, hemoglobin A_{1c} level, phosphorus level, high-sensitivity troponin T level, NT-proBNP level, fibroblast growth factor 23 level, eGFR, and proteinuria, severe CAC (score >100) was significantly associated with heart failure and composite cardiovascular disease. Furthermore, log CAC score was significantly and independently associated with higher risk of cardiovascular disease, myocardial infarction, and heart failure in multiple adjusted models (Table 2).

In addition, among 528 participants with a history of cardiovascular disease, CAC was significantly and independently associated with cardiovascular disease and all-cause mortality. For 1 SD higher level of log CAC scores, the hazard ratio was 1.29 (95% CI, 1.05-1.58; $P = .02$) for cardiovascular disease, 2.10 (95% CI, 1.34-3.29; $P = .001$) for myocardial infarction, and 1.63 (95% CI, 1.29-2.07; $P < .001$) for all-cause mortality after adjusting for the above-mentioned established and novel cardiovascular disease risk factors (eTable 1 in the Supplement). In the pooled analyses including all participants, the associations of CAC with cardiovascular disease and all-cause mortality were even stronger (eFigure 2 and eTable 2 in the Supplement). For 1 SD higher level of log CAC scores, the hazard ratio was 1.38 (95% CI, 1.20-1.59; $P < .001$) for cardiovascular disease, 1.69 (95% CI, 1.28-2.23; $P < .001$) for myocardial infarction, 1.42 (95% CI, 1.19-1.69; $P < .001$) for heart failure, and 1.35 (95% CI, 1.15-1.60; $P < .001$) for all-cause mortality after adjusting for multiple established and novel risk factors.

Inclusion of CAC score improved risk predictions for cardiovascular disease, myocardial infarction, heart failure, and all-cause mortality over use of the ACC/AHA atherosclerotic cardiovascular disease risk predictors (eTable 3 in the Supplement). Furthermore, the C statistics were significantly improved for prediction of cardiovascular disease, myocardial

Table 1. Baseline Characteristics of Chronic Renal Insufficiency Cohort Study Participants Without a History of Cardiovascular Disease by Coronary Artery Calcification Score Category

	Coronary Artery Calcification Score Category, No. (%)[a]			
	0 (None) (n = 618)	>0-100 (Moderate) (n = 460)	>100 (Severe) (n = 463)	*P* Value
Age, mean (SD), y	51.2 (12.4)	58.7 (10.5)	63.6 (8.2)	<.001
Male	258 (41.7)	250 (54.3)	302 (65.2)	<.001
Race/ethnicity				
Non-Hispanic white	271 (43.9)	199 (43.3)	221 (47.7)	.69
Non-Hispanic black	209 (33.8)	147 (32.0)	137 (29.6)	
Hispanic	107 (17.3)	90 (19.6)	79 (17.1)	
Other	31 (5.0)	24 (5.2)	26 (5.6)	
High school education	517 (83.7)	377 (82.1)	372 (80.3)	.37
Physical activity, mean (SD), MET/wk	247.6 (197.9)	214.3 (154.4)	190.4 (135.3)	<.001
Current cigarette smoking	49 (7.9)	43 (9.3)	46 (9.9)	.49
Consume alcohol weekly	143 (23.2)	101 (22.0)	103 (22.3)	.88
Body mass index, mean (SD)[b]	30.2 (6.9)	31.2 (6.2)	31.1 (6.1)	.02
Medication use				
Antihypertensive drugs	498 (80.7)	407 (88.9)	441 (95.7)	<.001
Lipid-lowering agents	263 (42.6)	264 (57.6)	337 (73.1)	<.001
History				
Diabetes	179 (29.0)	189 (41.1)	278 (60.0)	<.001
Hypertension	462 (74.9)	400 (87.1)	432 (93.3)	<.001
Laboratory values				
Systolic blood pressure, mean (SD), mm Hg	121.7 (19.5)	125.5 (19.6)	128.6 (21.0)	<.001
High-sensitivity CRP, median (IQR), mg/L	2.15 (0.89-4.89)	2.08 (0.94-5.52)	2.22 (0.98-5.05)	.59
Cholesterol, mean (SD), mg/dL				
Total	195.9 (45.5)	190.6 (43.3)	181.5 (41.1)	<.001
High-density lipoprotein	52.5 (17.6)	48.8 (15.3)	47.8 (14.9)	<.001
Low-density lipoprotein	110.7 (36.1)	106.6 (33.3)	98.8 (32.4)	<.001
Hemoglobin A_{1c}, mean (SD), %	6.05 (1.31)	6.28 (1.28)	6.65 (1.55)	<.001
Calcium, mean (SD), mg/dL	9.31 (0.52)	9.35 (0.52)	9.35 (0.53)	.38
Phosphorus, mean (SD), mg/dL	3.63 (0.64)	3.64 (0.62)	3.73 (0.69)	.03
Calcium phosphorus product, mean (SD), mg^2/dL^2	33.8 (6.1)	34.0 (5.8)	34.8 (6.3)	.02
Total parathyroid hormone, mean (SD), pg/mL	70.7 (75.7)	68.9 (57.2)	76.4 (74.1)	.24
Alkaline phosphatase, mean (SD), U/L	87.5 (31.3)	91.9 (33.8)	91.5 (37.3)	.06
High-sensitivity troponin T, median (IQR), pg/mL	5.90 (1.50-12.40)	9.12 (4.56-16.90)	12.40 (7.26-24.10)	<.001
N-terminal pro-B-type natriuretic peptide, median (IQR), pg/mL	81.3 (36.9-179.7)	98.1 (45.8-215.7)	131.5 (61.5-319.2)	<.001
Fibroblast growth factor 23, median (IQR), RU/mL	112.7 (76.5-187.2)	121.8 (84.4-187.1)	137.3 (94.3-209.2)	<.001
Estimated glomerular filtration rate, mean (SD), mL/min/1.73 m^2	49.9 (20.3)	46.5 (16.7)	41.9 (14.9)	<.001
Urinary protein, median (IQR), g/24 h	0.14 (0.06-0.93)	0.14 (0.07-0.80)	0.20 (0.08-0.98)	.06

Abbreviations: CRP, C-reactive protein; IQR, interquartile range; MET, metabolic equivalent.

SI conversion factors: To convert alkaline phosphatase to μkat/L, multiply by 0.0167; calcium to mmol/L, multiply by 0.25; HDL, LDL, and total cholesterol to mmol/L, multiply by 0.0259; and phosphorus to mmol/L, multiply by 0.323.

[a] Data are expressed as No. (%) unless otherwise indicated.

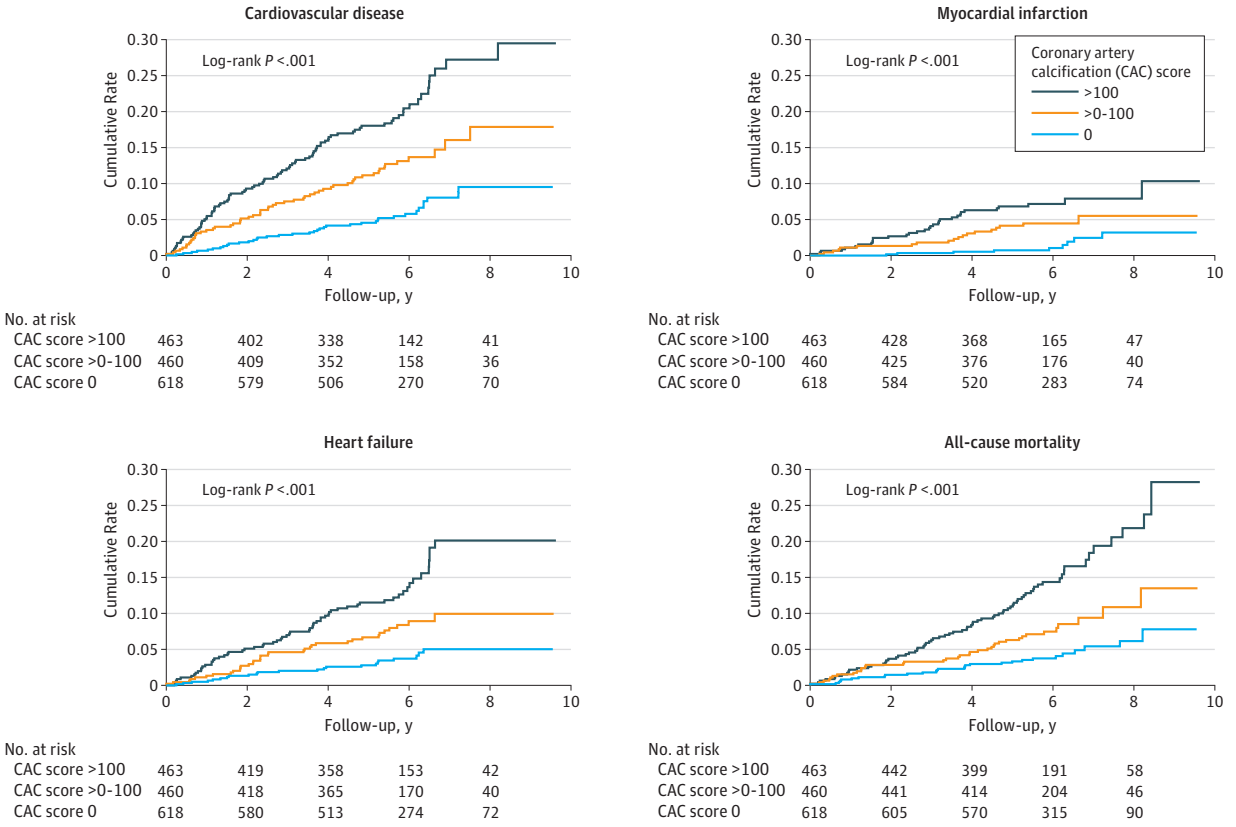
[b] Calculated as weight in kilograms divided by height in meters squared.

infarction, and heart failure but not for all-cause mortality when CAC score was added to the full prediction model, which included the ACC/AHA atherosclerotic cardiovascular disease risk predictors and novel risk factors. The change in C statistic was 0.02 (95% CI, 0-0.09; $P < .001$) for cardiovascular disease, 0.02 (95% CI, 0-0.09; $P = .03$) for myocardial infarction, and 0.01 (95% CI, 0-0.09; $P = .009$) for heart failure.

During 5 years of follow-up, the C statistic for continuous net reclassification improvement in CAC was 0.47 (95% CI, 0.14-0.77) for cardiovascular disease, 0.55 (95% CI, 0.14-0.78) for myocardial infarction, and 0.36 (95% CI, 0.14-0.77) for heart failure; all 3 were significant and reflect moderately strong improvements. There were similar results for integrated discrimination improvement with a C statistic of 0.02 (95% CI, 0.01-0.06) for cardiovascular disease, 0.01 (95% CI, 0.01-0.06) for myocardial infarction, and 0.01 (95% CI, 0.01-0.06) for heart failure; all 3 were significant improvements compared with the full prediction model.

Cardiovascular disease incidence and all-cause mortality significantly increased with ACC/AHA atherosclerotic cardio-

Figure 2. Kaplan-Meier Cumulative Event Rate of Cardiovascular Disease, Myocardial Infarction, Heart Failure, and All-Cause Mortality According to Coronary Artery Calcification Score Among Chronic Renal Insufficiency Cohort Participants Without a History of Cardiovascular Disease



A score of 0 indicates no coronary artery calcification; greater than 0 to 100, moderate calcification; greater than 100, severe calcification. Cardiovascular disease included myocardial infarction, heart failure, and stroke.

vascular disease risk scores (eFigure 3 in the Supplement). Within each ACC/AHA atherosclerotic cardiovascular disease risk score category (ie, <5.0%, 5.0%-7.5% and >7.5%), cardiovascular disease risk significantly increased at higher CAC levels after adjusting for sex, race/ethnicity, and clinic sites (**Figure 3**).

Discussion

The findings from the CRIC study indicate that CAC is strongly and significantly associated with risk of subsequent cardiovascular disease, myocardial infarction, heart failure, and all-cause mortality in patients with CKD. These relationships are graded and independent of the ACC/AHA atherosclerotic cardiovascular disease risk factors, as well as education level, BMI, physical activity, high-sensitivity CRP, hemoglobin A_{1c} level, phosphorus level, high-sensitivity troponin T level, NT-proBNP level, fibroblast growth factor 23 level, eGFR, and proteinuria. Furthermore, CAC scores improve risk prediction of future cardiovascular disease, myocardial infarction, and heart failure over use of the ACC/AHA atherosclerotic cardiovascular disease risk factors and other important novel cardiovascular disease risk factors in patients with CKD; however, the changes in the C statistic are small.

These findings have important clinical and public health implications because cardiovascular disease is the major cause of premature death in patients with CKD.[1-4] Coronary artery calcification is accelerated in patients with CKD due to 2 distinct pathological processes that result in medial (arteriosclerosis) and intimal (atherosclerosis) deposition.[21] Although there are data indicating that very high CAC scores may be associated with increased risk of death in patients undergoing hemodialysis, the average CAC scores in most patients are elevated at a level at which discriminatory power may be reduced.[22] Furthermore, there are fewer data available for dialysis-naive patients with CKD, for whom it is uncertain whether CAC score confers an elevated risk of cardiovascular disease events and all-cause mortality.[10]

Our study indicated that CAC was strongly and independently associated with the incidence of cardiovascular disease events and all-cause mortality among dialysis-naive patients with CKD. Plaque assessment by coronary CT angiography has shown some promise in predicting cardiovascular disease outcomes among patients with CKD.[23-25] In our study, inclusion of CAC score in the prediction models led to

Table 2. Multivariable-Adjusted Hazard Ratios for Cardiovascular Disease and Death Associated With Coronary Artery Calcification Among Chronic Renal Insufficiency Cohort Study Participants Without a History of Cardiovascular Disease

Coronary Artery Calcification Score Categories	Model 1[a]		Model 2[b]		Model 3[c]	
	Hazard Ratio (95% CI)	*P* Value for Trend	Hazard Ratio (95% CI)	*P* Value for Trend	Hazard Ratio (95% CI)	*P* Value for Trend
Cardiovascular Disease[d]						
0 (none)	1 [Reference]		1 [Reference]		1 [Reference]	
>0-100 (moderate)	2.40 (1.56-3.70)	<.001	2.02 (1.31-3.12)	<.001	1.60 (1.01-2.53)	.03
>100 (severe)	4.04 (2.63-6.20)		2.52 (1.63-3.89)		1.81 (1.16-2.82)	
Per 1 SD log[e]	2.08 (1.73-2.50)	<.001	1.66 (1.38-2.00)	<.001	1.40 (1.16-1.69)	<.001
Myocardial Infarction						
0 (none)	1 [Reference]		1 [Reference]		1 [Reference]	
>0-100 (moderate)	2.94 (1.29-6.71)	<.001	2.62 (1.14-6.01)	.02	1.39 (0.60-3.25)	.26
>100 (severe)	4.73 (2.10-10.7)		3.12 (1.36-7.16)		1.91 (0.85-4.28)	
Per 1 SD log[e]	2.12 (1.53-2.94)	<.001	1.70 (1.22-2.38)	.002	1.44 (1.02-2.02)	.04
Heart Failure						
0 (none)	1 [Reference]		1 [Reference]		1 [Reference]	
>0-100 (moderate)	2.38 (1.37-4.13)	<.001	2.02 (1.16-3.52)	.001	1.60 (0.87-2.93)	.05
>100 (severe)	4.35 (2.53-7.46)		2.82 (1.63-4.88)		2.03 (1.14-3.61)	
Per 1 SD log[e]	2.07 (1.65-2.60)	<.001	1.67 (1.32-2.10)	<.001	1.39 (1.10-1.76)	.006
All-Cause Mortality						
0 (none)	1 [Reference]		1 [Reference]		1 [Reference]	
>0-100 (moderate)	1.60 (0.96-2.67)	<.001	1.30 (0.76-2.20)	.002	1.08 (0.61-1.91)	.36
>100 (severe)	2.93 (1.80-4.78)		2.25 (1.36-3.73)		1.42 (0.82-2.46)	
Per 1 SD log[e]	1.64 (1.33-2.02)	<.001	1.46 (1.17-1.82)	<.001	1.19 (0.94-1.51)	.15

[a] Adjusted for age, sex, race, and clinical site.

[b] Adjusted for model 1 plus American College of Cardiology/American Heart Association atherosclerotic cardiovascular disease risk factors of age, sex, race, clinical site, total cholesterol level, high-density lipoprotein cholesterol level, systolic blood pressure, use of antihypertensive treatment, current cigarette smoking, and diabetes status.

[c] Adjusted for model 2 plus education level, body mass index, physical activity, log high-sensitivity C-reactive protein, hemoglobin A_{1c} level, phosphorus level, log high-sensitivity troponin T level, log N-terminal pro-B-type natriuretic peptide level, log fibroblast growth factor 23 level, estimated glomerular filtration rate, and log 24-hour urinary protein.

[d] Cardiovascular disease included myocardial infarction, heart failure, and stroke.

[e] One SD log is equal to 2.8.

a significant increase in the C statistic and positive net reclassification improvement and integrated discrimination improvement over use of ACC/AHA atherosclerotic cardiovascular disease risk factors and other novel risk factors. These findings suggest that CAC could be used for risk stratification and prediction among patients with CKD.

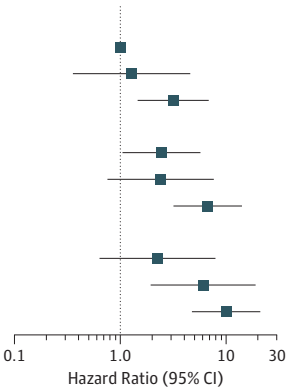
Although it is well documented that CAC predicts the risk of cardiovascular disease, myocardial infarction, and heart failure in the general population,[8,26] few prospective cohort studies have examined these associations in patients with CKD.[11,27] Russo et al[26] reported that a CAC score greater than 100 was associated with an 8.4-fold (95% CI, 2.3- to 30-fold; $P = .001$) higher risk of cardiovascular disease events (cardiac death and myocardial infarction) compared with those with a CAC score of 100 or less among 181 dialysis-naive patients with CKD. In 1284 patients with CKD in stages 1, 2, or 3 from the Multi-Ethnic Study of Atherosclerosis, a 1 SD higher CAC score was associated with a hazard ratio of 1.69 (95% CI, 1.45-1.97) for cardiovascular disease after adjusting for the Framingham risk predictors.[11]

The CRIC study is the largest prospective cohort study among dialysis-naive patients with CKD to examine the association between baseline CAC score and subsequent risk of cardiovascular disease, myocardial infarction, and heart failure. In addition, there was adjustment for ACC/AHA atherosclerotic cardiovascular disease risk predictors and important novel cardiovascular disease risk factors among patients with CKD. Our study supports an independent association between CAC scores and the risk of cardiovascular disease, myocardial infarction, and heart failure.

The underlying pathological process of CAC in patients with CKD may be somewhat different compared with patients without CKD.[21,27] Previous studies suggested that serum levels of calcium and phosphorus were associated with risk of CAC independent of traditional risk factors in patients with CKD.[5,27] High intracellular phosphorus promotes the mineralization of vascular smooth muscle cells and medial artery calcification.[28,29] Medial artery calcification is more prevalent in patients with CKD[30,31] even though the atherosclerotic intimal calcification associated with cellular necrosis, inflammation, lipid deposition, and vascular occlusion is also present in patients with CKD.[32] Medial artery calcification causes arterial stiffness, left ventricular hypertrophy, a decrease in coronary artery perfusion, and impairment of collateral circulation formation, which leads to adverse outcomes.[33,34] Both intimal and medial artery calcification were associated with total and cardiovascular disease mortality in patients with CKD receiving dialysis.[35]

Figure 3. Multivariable-Adjusted Hazard Ratios of Cardiovascular Disease by ACC/AHA Atherosclerotic Cardiovascular Disease Risk Score and CAC Score Among Chronic Renal Insufficiency Cohort Participants Without a History of Cardiovascular Disease

ACC/AHA Atherosclerotic Cardiovascular Disease Risk Score Category	Hazard Ratio (95% CI)
<5.0%	
CAC score 0	1 [Reference]
CAC score >0-100	1.28 (0.36-4.60)
CAC score >100	3.16 (1.46-6.84)
5.0%-7.5%	
CAC score 0	2.45 (1.05-5.71)
CAC score >0-100	2.41 (0.76-7.64)
CAC score >100	6.70 (3.18-14.10)
>7.5%	
CAC score 0	2.25 (0.64-7.93)
CAC score >0-100	6.09 (1.94-19.10)
CAC score >100	10.00 (4.76-21.00)



Error bars indicate 95% CIs; ACC, American College of Cardiology; AHA, American Heart Association; CAC, coronary artery calcification. A CAC score of 0 indicates no calcification; greater than 0 to 100, moderate calcification; greater than 100, severe calcification.

The findings from the CRIC study suggest that CAC score is associated with excess risk of cardiovascular disease, myocardial infarction, and heart failure independent of atherosclerotic and mineral and bone metabolism factors. Our findings warrant further investigation on novel mechanisms of CAC related to cardiovascular disease in patients with CKD. In addition, clinical trials of the prevention and treatment of CAC by maintaining normal phosphorus homeostasis on the risk of cardiovascular disease are warranted.

Limitations

Several limitations of this study should be noted. First, we are unable to differentiate intima vs media calcification due to limitations in the methods used to measure CAC in this study. Second, there are relatively small numbers of events within each CAC score category for clinical outcomes, potentially contributing to the statistical insignificance of the association of CAC score categories with cardiovascular disease. However, continuous CAC score was significantly associated with cardiovascular disease.

In addition, cause-specific mortality data from out-of-hospital deaths are not currently available. Therefore, out-of-hospital cardiovascular disease deaths were not included in this analysis, which could reduce the statistical power. A majority of participants (56%) were taking statins during the study, which would weaken the observed association.

Conclusions

Coronary artery calcification is independently and significantly related to the risks of cardiovascular disease, myocardial infarction, and heart failure in patients with CKD. In addition, CAC improves risk prediction for cardiovascular disease, myocardial infarction, and heart failure over use of established and novel cardiovascular disease risk factors among patients with CKD; however, the changes in the C statistic are small.

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