Title

Relation of aortic valve calcium to chronic kidney disease (from the Chronic Renal Insufficiency Cohort Study)

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Aortic Valve Calcification among Patients with CKD: Results from CRIC Study

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Abstract

Background: Although subjects with chronic kidney disease (CKD) are at markedly increased risk for cardiovascular mortality, the impact of CKD on aortic valve calcification (AVC) has not been fully elucidated. Also, few data are available on the relationship of AVC and earlier stages of CKD. We sought to assess the relationship of AVC with eGFR, traditional and novel cardiovascular risk factors, and markers of bone metabolism in the Chronic Renal Insufficiency Cohort (CRIC) Study.

Methods: All patients who underwent aortic valve scanning in the CRIC study were included. The relationship between AVC and eGFR, traditional and non-traditional cardiovascular risk factors, and markers of calcium metabolism were analyzed using both adjusted and unadjusted regression models.

Results: A total of 1964 CRIC baseline participants underwent CT for AVC quantification. AVC was inversely associated with eGFR ($P<0.001$), and there was a graded relationship between decreased renal function and increased levels of AVC. Adjusted regression models identified several traditional and novel risk factors for AVC in patients with CKD. There was a difference in AVC risk factors between black and non-black patients.

Conclusions: Our study shows that eGFR is a risk factor for AVC in patients with CKD, which is independent of traditional cardiovascular risk factors.

Introduction

Aortic valve calcification (AVC) is a common cardiovascular disease affecting 26% of individuals age 65 and older. This risk increases to 35% in patients between 75 and 84 and is as high as 50% in individuals over the age of 80 in the United States of America.[1] The development of hydroxyapatite crystals and lamellar bone formation in end-stage aortic valve calcific disease is promulgated by valve type (i.e. bicuspid valve) and proatherosclerotic risk factors such as hypertension, hypercholesterolemia, diabetes mellitus and cigarette smoking. Derangements in bone metabolism, such as those seen in hyperparathyroidism or kidney disease, may contribute to or exacerbate the pathologic processes that lead to AVC and ensuing stenosis.

Patients with chronic kidney disease (CKD) have increased cardiovascular morbidity and mortality. Given the rising prevalence of CKD, there has been a recent focus on understanding the contribution of CKD to cardiovascular pathology including AVC. Clinical studies indicate that the prevalence and progression of aortic valve calcification is increased in patients with end-stage renal disease (ESRD) and that derangements in bone metabolism may play a role in the pathophysiology of aortic sclerosis in these patients. [2, 3] The prevalence of AVC in patients with earlier stages of CKD, however, is not known. Subgroup analyses of large cardiovascular trials such as the Multi-ethnic Study of Atherosclerosis (MESA) have had insufficient power to identify an association between aortic valve calcification and CKD.[4, 5] The role of traditional and novel cardiovascular risk factors in patients with CKD has also not been fully explored; and the impact of CKD and its associated metabolic disturbances such as osteodystrophy and calcium, phosphorus, and parathyroid hormone abnormalities on aortic valve calcification is unknown.

The Chronic Renal Insufficiency Cohort (CRIC) study is a large prospective epidemiological study of patients with varying degree of CKD.[6] All CRIC study participants

underwent assessment for aortic valve calcification by medical history and measurement of calcium on electron beam computed tomography (EBT). In this analysis, we examine the relationship between impaired renal function and AVC and explore the role of various traditional and novel cardiovascular risk factors, as well as markers of bone metabolism on AVC in patients with CKD.

Methods

Study Population

The CRIC Study population is a racially and ethnically diverse cohort of men and women aged 21 to 74 years with mild-to-moderate renal disease; approximately half of which have diabetes. The CRIC participants were recruited between May 2003 and August 2008 from seven clinical centers in the United States of America.[6] The identification of subjects was facilitated through searches of laboratory databases, medical records, and referrals from health care providers. Subjects with cirrhosis, HIV infection, polycystic kidney disease, or renal cell carcinoma, as well as those on dialysis or recipients of a kidney transplant, or those taking immunosuppressant drugs were excluded from study participation. An eGFR entry criteria (20-70 mL/min/1.73m^2) was used as an enrolledment criteria to limit the proportion of older individuals who were recruited with age-related diminutions of GFR but otherwise non-progressive CKD. A total of 1,964 CRIC participants were included in the final analysis.

This study was approved by the Institutional Review Boards from each of the participating clinical centers as well as the scientific and data coordinating center. A written informed consent was obtained from all participants. This study also conformed

to the Health Insurance Portability and Accountability Act (HIPAA) guidelines.

Measures of Kidney Function

Estimated glomerular filtration rate (eGFR) was computed using the Modification of Diet in Renal Disease (MDRD) Study equation.[7] CKD was defined as eGFR < 60 ml/min/1.73m2 based on the National Kidney Foundation's KDOQI (Kidney disease Outcome Quality Initiative) guidelines.

~~Electron Beam~~ Computed Tomography Imaging

All CRIC participants included in this analysis underwent baseline non-contrast CT scans, which were analyzed for both coronary artery and aortic valve calcium. Spatial resolution for each system was 1.15 mm_3 for multi-detector detector row CT (0.68 x 0.68 x 2.50 mm) and 1.38 mm_3 for electron-beam CT (0.68 x 0.68 x 3.00 mm).~~Spatial resolution was 1.38 mm^3 for EBCT (0.68 x 0.68 x 3.00 mm).~~ Full details concerning the equipment, scanning methods, and CT quality control in CRIC, including results of CAC associations with GFR have been reported previously.[8]

All scans were sent to a central CRIC CT reading center (Harbor-UCLA Research and Education Institute, Los Angeles, CA). Calcium strongly attenuates x-rays, appears bright on CT scans, and is readily differentiated from surrounding tissue. All scans were analyzed with a commercially available software package (Neo Imagery Technologies, City of Industry, California). An attenuation threshold of 130 Hounsfield units and a minimum of 3 contiguous pixels were utilized for identification of a calcific lesion. Each focus exceeding the minimum criteria was scored using the algorithm developed by Agatston et al,[9] calculated by multiplying the lesion area by a density factor derived from the maximal Hounsfield unit (Hu) within this area. The density factor was assigned in the following manner: 1

for lesions with peak attenuation of 130-199 Hu, 2 for lesions with peak attenuation of 200-299 Hu, 3 for lesions with peak attenuation of 300-399 Hu, and 4 for lesions with peak attenuation >400 Hu.

Consistent with prior methodology,[10-12] a lesion was classified as aortic valve calcium (AVC) if it resided within the aortic valve leaflets, exclusive of the aortic annulus, aortic sinuses, aortic wall, or coronary arteries, and if there were 3 contiguous pixels of at least 130 Hounsfield units in brightness. ~~For each individual lesion, calcium content was quantified by the Agatston method;[9] s~~Single lesion measurements were then summed to give a total Agatston score. If no lesions reached threshold values, the Agatston score was recorded as zero.

Statistical Analysis

Multiple logistic regression analyses were used to examine the cross-sectional association between traditional and novel risk factors and aortic valve calcification.

Results

Table 1 summarizes demographics and baseline characteristics from the CRIC database participants who underwent baseline CT with calcium scoring of their aortic valves (n=1964). The participants were grouped based on the presence and severity of aortic valve calcification. Approximately half of the participants had no calcification of the aortic valve or the annulus (AVC and AVRING = 0, n = 1023). The remainder had some calcification with 26% (AVC + AVRING >0-100, n=514) and 22% (AVC + AVRING > 100, n =427) showing mild versus more significant disease, respectively. An unadjusted regression analysis was used to examine the

relationship between several traditional and novel risk factors and AVC. Increasing age, BMI, waist circumference, blood pressure, cholesterol, hemoglobin A1c, and decreased physical activity were all independently associated with aortic valve calcification. There was also a significant association between valve calcification and a history of diabetes, hypertension, or cardiovascular disease (CVD). Novel cardiovascular risk factors such as hs-CRP, uric acid, total plasma homocysteine, and Lpa were also associated with increased AVC. The average eGFR of the cohort was 44.6 ml/min/1.73 m2, and decreased eGFR was associated with increased AVC ($p<0.0001$). Figure 1 illustrates this inverse relationship between eGFR and aortic valve calcification across the study population. Additionally, patients with more significant aortic valve calcification also had higher levels of phosphate and parathyroid hormone and lower hemoglobin levels.

Table 2 summarizes the graded relationship between stage of CKD and increased AVC ($p=0.0082$). Patients with more significant renal impairment had greater prevalence or AVC and more severe AVC with a higher burden of calcification. A clear difference in prevalence and severity of calcification was noted between patients with stage 3A and stage 3B CKD, reinforcing the heterogeneity of cardiovascular morbidity in patients with eGFR 30-60.

Adjusted regression models were used to examine the role of risk factors identified in the initial unadjusted regression model in a step-wise manner (Table 3). Model 1 examined traditional cardiovascular risk factors and identified age, race, history of cardiovascular disease, diabetes, systolic blood pressure, high cholesterol, and low HDL as independent predictors of more severe aortic valve calcification. EGFR was also an independent risk factor for aortic valve calcification in this model. Of these risk

factors, age and hyperlipidemia were the strongest predictors of more significant AVC with odds ratios of 6.06 and 2.43, respectively. A second model added novel cardiovascular risk factors to the traditional risk factors. CRP and plasma homocysteine were additional independent predictors of aortic valve calcification. In this analysis, Lp(a) and uric acid were not independent predictors of aortic valve calcification. Furthermore, when adjusted for these novel risk factors, EGFR was no longer an independent predictor of AVC burden. A third model incorporated markers of bone metabolism identified in the initial unadjusted model, calcium, phosphate, and parathyroid hormone. These were not independent predictors of AVC.

Race was an independent predictor of AVC in all adjusted regression models with black patients having decreased odds ratio of presence and severity of AVC. Risk factors were examined independently for black and non-black patients in Table 4. Age, high systolic blood pressure, homocysteine levels, and the presence of diabetes were strong predictors of AVC severity in both groups. However, a history of cardiovascular disease, high cholesterol and LDL, and high CRP levels were risk factors for more severe AVC in non-black patients but not in black patients.

Discussion

To our knowledge this study is the first to show a statistically significant correlation between non-end stage CKD and aortic valve calcification and to identify associations between the traditional and non-traditional cardiovascular risk factors and derangements in bone metabolisms and AVC in patients with early stages of CKD. In addition to confirming the relationship between traditional cardiovascular risk factors and

increased AVC in patients with CKD, the unadjusted regression analysis also identified decreased eGFR as a significant risk factor for AVC. Derangements in bone metabolism, including increased PTH and Ph levels, were associated with AVC. Novel cardiovascular risk factors including hs-CRP, total plasma homocysteine, Lp(a), and uric acid, which are elevated in patients with CKD,[13] are also associated with AVC.

The adjusted regression models further examined the relationship between traditional, novel, and bone metabolism risk factors of AVC. When adjusted for traditional cardiovascular risk factors, eGFR remained an independent risk factor for AVC, suggesting that patients with CKD are at increased risk relative to an age-matched patient with similar Framingham risk profile. However, when novel cardiovascular risk factors such as homocysteine and CRP are included in the model, eGFR was no longer an independent risk factor. Similarly, markers of bone metabolism were also not independently associated with AVC when novel cardiovascular risk factors were included in the analysis. These results suggest that the risk of AVC imparted by decreased kidney function may be in part accounted for by increased homocysteine and CRP, reflecting altered methionine metabolism or methylation state and a systemic inflammatory milieu in these patients.

Markers of bone metabolism, including serum phosphate and parathyroid hormone were also associated with increased AVC in the unadjusted model. Other analyses have also shown that elevated phosphate levels are associated with AVC.[14] Furthermore, the ADVANCE and EVOLVE trials sought to affect vascular calcification and cardiovascular events, respectively, by targeting parathyroid hormone axis with addition of cinacalcet in patients with ESRD on hemodialysis. Though vascular and

valvular calcification was decreased, this did not translate into improved cardiovascular outcomes.[15, 16] Our analysis suggests that in patients with CKD, serum phosphate and parathyroid hormone levels are not independent predictors of AVC when incorporated into a model that includes traditional and novel cardiovascular risk factors.

Significant ethnic differences in the risk factors for AVC were also noted. Several risk factors such as hypertension, diabetes, age, and homocysteine level increased AVC in both black and non-black patients. However, there were several risk factors that were unique to non-black patients, including a history of cardiovascular disease and high cholesterol, LDL, and CRP levels.

These correlations raise interesting hypotheses about the mechanism of valve calcification in different populations and suggest heterogeneity in the pathogenesis of AVC. AVC may not be a stereotyped single process, but instead may represent different pathologic mechanisms that result in the similar end of aortic valve sclerosis and calcification with ensuing stenosis.

The study has several limitations including the use of eGFR rather than direct measure of GFR. However, eGFR is an accepted and commonly used surrogate for GFR in clinical practice. The cross-sectional design does not provide insight data on disease progression or clinical outcomes. Though this study revealed a correlation between CKD and AVC and identified several relevant risk factors, which may be contributing to the pathophysiology of AVC in CKD patients, future studies are needed to determine the rate of progression of AVC in patients with CKD and the role of different risk factors in progression. This study focused on AVC as detected by CT, however the calcium load on the valve is not always predictive of clinical stenosis or

disease progression. Using echocardiography to understand the functional result of AVC will yield a deeper understanding of the relationship between calcification and disease in patients with CKD.

Table 1. Baseline characteristics of study participants by aortic valve calcification. Total AVC includes both aortic valve and aortic valve ring calcification. The 24 hour urine protein, albumin, hs-CRP, total PTH, serium vit D, and lipoprotein A are presented as both original levels and median with interquartile range. Data was taken from the EBT visit, if available, or from the initial baseline visit. Data taken at baseline includes Phosphate, total PTH, Lipoprotein A, plasma homocysteine, hs-CRP, 24 hour albumin,

	n (%) or Mean (StdDev)				
			By AVC		
	All with AVC Measured n=1964	*AVC and AVRING both =0 n=1023*	*Total AVC >0 - 100 n=514*	*Total AVC >100 n=427*	*p*
Demographics					.
Participant Age	58.45 (11.45)	53.16 (11.73)	62.26 (7.90)	66.52 (6.99)	<.0001
Female	918 (47%)	466 (46%)	261 (51%)	191 (45%)	0.0983
Male	1046 (53%)	557 (54%)	253 (49%)	236 (55%)	.
Race / ethnicity					.
Hispanic and Other	445 (23%)	247 (24%)	109 (21%)	89 (21%)	0.1941
Non-Hispanic Black	670 (34%)	340 (33%)	192 (37%)	138 (32%)	.
Non-Hispanic White	849 (43%)	436 (43%)	213 (41%)	200 (47%)	.
Self-reported history of CVD, n(%)					.
Cardio-Vascular Disease (Yes/Not Yes)	494 (25%)	169 (17%)	149 (29%)	176 (41%)	<.0001
Traditional Cardiovascular Risk Factors					.
Current Smoker	194 (10%)	111 (11%)	43 (8%)	40 (9%)	0.2820
Body Mass Index (kg/m^2)	31.13 (6.70)	30.57 (6.87)	31.72 (6.58)	31.73 (6.32)	0.0007
Waist Circumference (cm)	103.71 (15.83)	101.77 (16.32)	105.01 (15.53)	106.81 (14.31)	<.0001
Total METs (METhrs/week)	209.93 (145.91)	228.87 (161.28)	198.41 (125.71)	178.24 (120.80)	<.0001
Diabetes	917 (47%)	384 (38%)	280 (54%)	253 (59%)	<.0001
Glucose (mg/dL)	113.80 (47.85)	110.24 (46.95)	118.76 (51.38)	116.39 (44.90)	0.0021
Hemoglobin A1C (%) at Baseline	6.50 (1.52)	6.33 (1.55)	6.74 (1.53)	6.64 (1.36)	<.0001
Diagnosis of Hypertension	1703 (87%)	816 (80%)	477 (93%)	410 (96%)	<.0001
Systolic BP (mmHg)	126.59 (21.25)	123.63 (20.35)	127.76 (22.01)	132.25 (21.19)	<.0001
Diastolic BP (mmHg)	70.55 (12.45)	73.22 (12.35)	68.65 (12.12)	66.43 (11.56)	<.0001

	n (%) or Mean (StdDev)				
		By AVC			
	All with AVC Measured n=1964	*AVC and AVRING both =0 n=1023*	*Total AVC >0 - 100 n=514*	*Total AVC >100 n=427*	*p*
Pulse Pressure	56.04 (18.56)	50.41 (16.47)	59.11 (18.07)	65.86 (18.97)	<.0001
High Cholesterol	1698 (86%)	834 (82%)	462 (90%)	402 (94%)	<.0001
Low-density Lipoprotein (mg/dL)	103.07 (34.82)	105.58 (34.81)	100.89 (35.00)	99.70 (34.22)	0.0040
High-density Lipoprotein (mg/dL)	48.97 (15.76)	49.27 (16.06)	50.13 (16.99)	46.84 (13.13)	0.0049
Triglycerides	154.61 (105.91)	155.52 (112.37)	151.41 (97.82)	156.28 (99.36)	0.7280
Kidney Function Measures					.
eGFR using CRIC equation	44.60 (17.58)	47.11 (18.94)	44.17 (16.32)	39.05 (13.96)	<.0001
24H Urine Protein (g/24H)	1.07 (2.16)	1.15 (2.24)	0.94 (2.01)	1.05 (2.16)	0.2423
Median (IQR)	0.17 (0.07 - 0.93)	0.18 (0.07 - 1.02)	0.15 (0.06 - 0.68)	0.18 (0.07 - 0.91)	0.0776
24H Urine Albumin (g/24H)	0.74 (1.76)	0.84 (1.93)	0.61 (1.39)	0.69 (1.74)	0.0489
Median (IQR)	0.05 (0.01 - 0.56)	0.06 (0.01 - 0.65)	0.04 (0.01 - 0.45)	0.05 (0.01 - 0.41)	0.3501
Novel Markers and Bone Metabolism					.
High Sensitivity CRP	4.64 (7.64)	4.18 (7.28)	4.85 (7.29)	5.47 (8.76)	0.0101
Median (IQR)	2.22 (0.94 - 5.23)	1.94 (0.87 - 4.69)	2.36 (0.96 - 5.97)	2.65 (1.14 - 6.04)	0.0001
Uric Acid (mg/dL) at Baseline	7.17 (1.88)	7.01 (1.89)	7.21 (1.87)	7.51 (1.85)	<.0001
Total Plasma Homocys (umol/L)	14.35 (5.62)	13.54 (5.03)	14.16 (4.86)	16.55 (7.06)	<.0001
CBC Hemoglobin (g/dL)	12.88 (1.79)	13.10 (1.83)	12.69 (1.69)	12.57 (1.72)	<.0001
Calcium (mg/dL)	9.31 (0.54)	9.30 (0.56)	9.30 (0.50)	9.33 (0.54)	0.5579
Phosphate (mg/dL)	3.70 (0.67)	3.66 (0.68)	3.75 (0.67)	3.73 (0.66)	0.0213
Total Parathyroid Hormone (pg/ml)	69.47 (70.19)	70.12 (68.65)	63.24 (49.16)	75.39 (91.52)	0.0294
Median (IQR)	50.00 (33.00 - 81.00)	50.00 (32.40 - 80.00)	47.00 (33.00 - 77.00)	54.10 (34.00 - 89.00)	0.0683
Serum 25(OH)-Total Vitamin D (ng/mL)	26.14 (14.35)	25.93 (14.14)	26.70 (14.73)	25.92 (14.40)	0.7290
Median (IQR)	23.85 (14.30 - 35.50)	23.75 (15.20 - 34.95)	24.20 (14.10 - 36.80)	24.00 (14.00 - 34.80)	0.7417
lipoprotein(a)(mg/dl)	36.70 (40.73)	34.51 (40.34)	38.71 (40.60)	39.51 (41.62)	0.0460
Median (IQR)	20.70 (7.40 - 54.40)	16.95 (7.10 - 47.80)	23.70 (8.30 - 61.00)	22.95 (7.90 - 61.30)	0.0119

Table 2. Prevalence and severity of aortic valve calcification by eGFR. eGFR from the EBT visit was used. Total aortic valve calcification (AVC) includes aortic valve and aortic valve ring calcification.

		eGFR (ml/min/1.73m2) at EBT Visit				
	All w EBT N = 1923	*<30 n = 418*	*30-<45 n = 622*	*45-<60 n = 507*	*>60 n = 376*	*p-value*
Total AVC						.
Mean (SD)	260.40 (656.56)	377.29 (984.05)	263.14 (555.17)	206.68 (512.07)	146.72 (427.63)	0.0082
Median	82	114	101	65	32	.
N (%)						.
0	1023 (52.1%)	205 (49%)	274 (44.1%)	264 (52.1%)	259 (68.9%)	<.0001
>0 to 100	514 (26.2%)	101 (24.2%)	173 (27.8%)	147 (29%)	85 (22.6%)	.
>100	427 (21.7%)	112 (26.8%)	175 (28.1%)	96 (18.9%)	32 (8.5%)	.

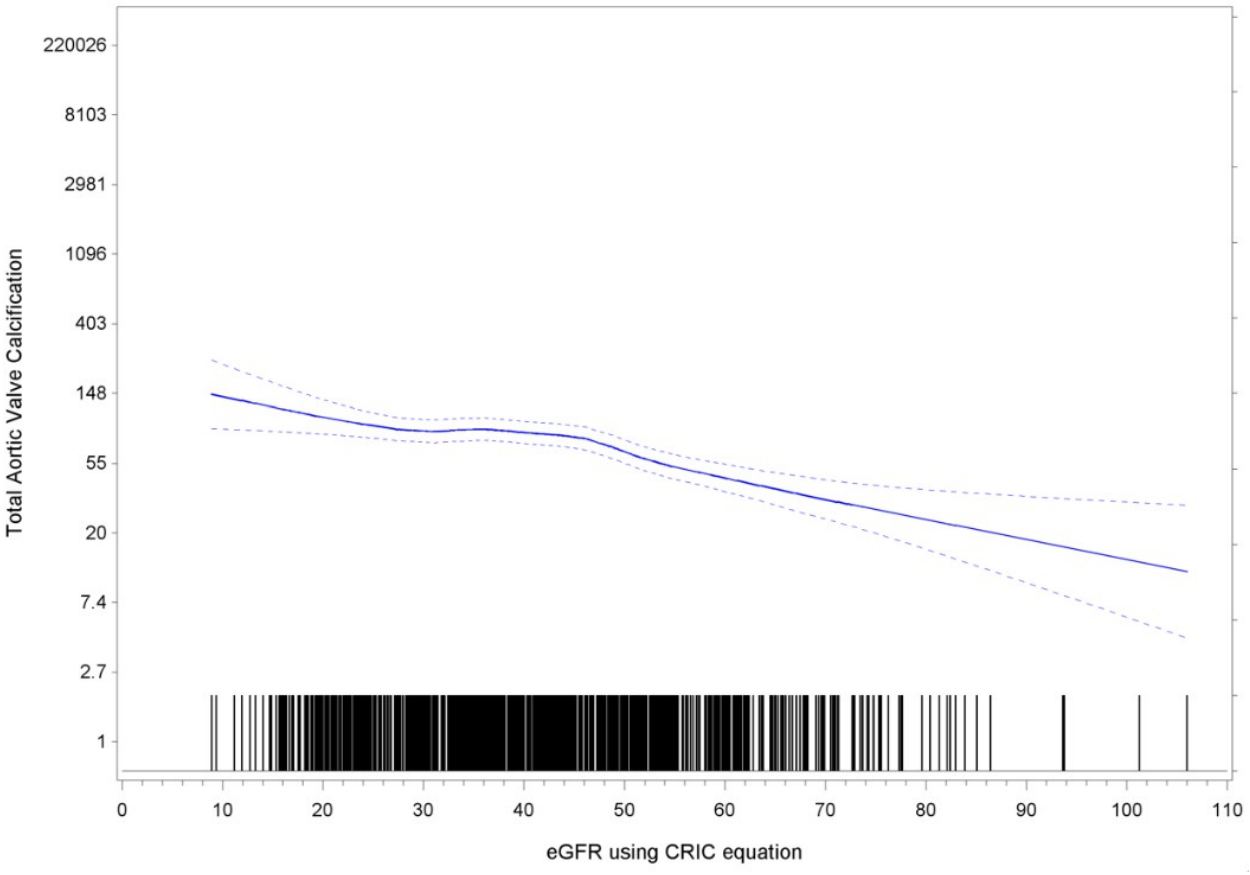
Table 3. **Adjusted logistic regression analysis of traditional (Model 1), novel (Model 2), and bone metaolism (Model 3) risk factors in patients with aortic valvce calcification.** Model 1 is adjusted for age, gender, race, self-reported history of CVD, smoking, BMI,waist circumference, total MET score at baseline, diabetes, hypertension, high cholesterol, low-density lipoprotein, high-density lipoprotein, 24hr urine protein, clinical site. Model 2 is adjusted for the covariates in Model 1 plus high sensitivity CRP, uric acid, total plasma homocysteine, and lipoprotein(a). Model 3 is adjusted for the covariates in Model 2 plus calcium, phosphate, and total parathyroid hormone.

	Model 1: Traditional CV risk factors			*Model 2: Novel CV risk factors*			*Model 3 : Markers of bone metabolism*		
	AVC >0 to 100	*AVC > 100*	*p*	*AVC >0 to 100*	*AVC > 100*	*p*	*AVC >0 to 100*	*AVC > 100*	*p*
eGFR using CRIC equation	1.08 (0.92, 1.27)	0.80 (0.65, 0.97)	0.015	1.14 (0.94, 1.40)	0.97 (0.76, 1.23)	0.297	1.12 (0.90, 1.39)	0.94 (0.72, 1.23)	0.406
Participant Age	2.87 (2.37, 3.48)	6.06 (4.66, 7.88)	<.001	3.04 (2.46, 3.76)	6.39 (4.76, 8.58)	<.001	3.17 (2.55, 3.95)	6.91 (5.09, 9.39)	<.001
Race/Ethnicity: Hispanic and Other	1.09 (0.65, 1.85)	1.22 (0.67, 2.21)	0.031	1.21 (0.69, 2.12)	1.49 (0.79, 2.83)	<.001	1.29 (0.73, 2.27)	1.45 (0.75, 2.81)	<.001
Non-Hispanic Black	0.92 (0.67, 1.27)	0.59 (0.41, 0.85)	.	0.67 (0.47, 0.97)	0.38 (0.25, 0.59)	.	0.68 (0.47, 1.00)	0.40 (0.26, 0.63)	.
Female	1.21 (0.90, 1.64)	0.95 (0.67, 1.36)	0.305	1.19 (0.84, 1.69)	1.07 (0.71, 1.60)	0.607	1.13 (0.78, 1.62)	1.01 (0.66, 1.56)	0.788
Cardiovascular Disease	1.41 (1.03, 1.93)	2.16 (1.55, 3.01)	<.001	1.26 (0.89, 1.77)	2.00 (1.38, 2.89)	<.001	1.18 (0.83, 1.67)	1.91 (1.32, 2.79)	0.002
Current Smoker	0.99 (0.63, 1.56)	1.32 (0.80, 2.20)	0.491	0.91 (0.55, 1.51)	0.94 (0.51, 1.73)	0.934	0.91 (0.55, 1.52)	0.90 (0.48, 1.67)	0.92
Body Mass Index	1.01 (0.97, 1.06)	1.01 (0.96, 1.06)	0.826	1.01 (0.97, 1.06)	1.00 (0.95, 1.05)	0.829	1.01 (0.97, 1.06)	1.00 (0.95, 1.05)	0.801
Waist Circumference	0.98 (0.75, 1.30)	1.09 (0.80, 1.50)	0.777	0.95 (0.70, 1.27)	1.04 (0.74, 1.47)	0.845	0.94 (0.69, 1.27)	1.04 (0.73, 1.47)	0.84
Total METs	0.99 (0.86, 1.14)	0.95 (0.79, 1.14)	0.865	1.03 (0.88, 1.19)	0.96 (0.78, 1.17)	0.793	1.03 (0.89, 1.20)	0.95 (0.78, 1.17)	0.729
Diabetes	1.89 (1.41, 2.54)	1.84 (1.31, 2.57)	<.001	1.99 (1.45, 2.75)	1.78 (1.22, 2.58)	<.001	1.86 (1.34, 2.60)	1.82 (1.24, 2.68)	<.001
Systolic Blood Pressure	1.00 (1.00, 1.01)	1.01 (1.00, 1.02)	0.012	1.01 (1.00, 1.02)	1.02 (1.01, 1.03)	0.002	1.01 (1.00, 1.02)	1.02 (1.01, 1.03)	0.002
High Cholesterol	1.66 (1.11, 2.49)	2.43 (1.40, 4.20)	0.002	1.96 (1.26, 3.07)	2.52 (1.39, 4.55)	0.001	2.02 (1.28, 3.20)	2.53 (1.38, 4.63)	0.001
Low-density Lipoprotein	0.99 (0.85, 1.14)	1.16 (0.99, 1.37)	0.113	0.96 (0.82, 1.13)	1.15 (0.96, 1.39)	0.137	0.96 (0.82, 1.13)	1.12 (0.93, 1.36)	0.248
High-density Lipoprotein	1.13 (0.98, 1.30)	0.92 (0.77, 1.09)	0.048	1.12 (0.95, 1.30)	0.93 (0.77, 1.14)	0.15	1.12 (0.95, 1.31)	0.95 (0.78, 1.16)	0.182
24 hour urine protein	1.05 (0.79, 1.40)	0.92 (0.66, 1.28)	0.715	1.01 (0.73, 1.40)	0.93 (0.63, 1.36)	0.896	0.95 (0.68, 1.33)	0.98 (0.66, 1.45)	0.962
High Sensitivity CRP				1.18 (0.97, 1.43)	1.37 (1.11, 1.71)	0.015	1.18 (0.97, 1.43)	1.35 (1.08, 1.69)	0.025
Uric Acid				1.01 (0.92, 1.10)	1.06 (0.96, 1.17)	0.472	1.00 (0.92, 1.10)	1.07 (0.97, 1.19)	0.348
Total Plasma Homocysteine				1.01 (0.98, 1.04)	1.08 (1.04, 1.12)	<.001	1.01 (0.98, 1.05)	1.08 (1.04, 1.12)	<.001
Lipoprotein(a)				1.13 (1.00, 1.27)	1.11 (0.96, 1.28)	0.128	1.13 (1.00, 1.28)	1.10 (0.96, 1.27)	0.136
Calcium							0.77 (0.56, 1.07)	1.03 (0.71, 1.49)	0.189
Phosphate							1.20 (1.01, 1.43)	1.06 (0.87, 1.31)	0.103
Total Parathyroid Hormone							0.81 (0.63, 1.06)	0.82 (0.61, 1.10)	0.24

Table 4. Odds ratio of aortic valve calcification associated with traditional and novel risk factors from logistic regression analysis by race. For the following continuous variables, the odds ratio is per standard deviation of the value: eGFR, age, waist circumference, total METs at baseline, LDL, HDL, and phosphate. The natural log of one plus the following continuous variables was used: hs-CRP, Lipoprotein a, total PTH, 24 hours urine protein. The following variables were from baseline measurements: Total Met, hsCRP, uric acid, homocysteine, Lipoprotein a, and total PTH.

	Odds Ratio >0 - 100		*Odds Ratio 100+*		*p*	
	Black	*Not Black*	*Black*	*Not Black*	*Black*	*Not Black*
eGFR using CRIC equation	1.00 (0.70, 1.43)	1.22 (0.91, 1.63)	0.93 (0.59, 1.45)	0.90 (0.63, 1.30)	0.941	0.208
Participant Age	3.76 (2.49, 5.68)	2.86 (2.18, 3.74)	7.36 (4.20, 12.89)	6.90 (4.68, 10.19)	<.001	<.001
Female	1.42 (0.75, 2.68)	1.00 (0.63, 1.59)	2.29 (1.09, 4.82)	0.72 (0.41, 1.28)	0.092	0.462
Cardio-Vascular Disease	1.42 (0.82, 2.46)	1.12 (0.69, 1.81)	1.23 (0.66, 2.29)	2.55 (1.54, 4.23)	0.459	<.001
Current Smoker	1.19 (0.57, 2.48)	0.72 (0.33, 1.55)	1.12 (0.47, 2.65)	0.61 (0.23, 1.60)	0.892	0.525
Body Mass Index	1.02 (0.95, 1.10)	1.00 (0.94, 1.06)	0.99 (0.91, 1.08)	0.98 (0.91, 1.05)	0.744	0.785
Waist Circumference	0.90 (0.55, 1.48)	1.00 (0.67, 1.49)	1.07 (0.62, 1.85)	1.17 (0.73, 1.89)	0.826	0.764
Total METs	1.02 (0.81, 1.29)	1.06 (0.86, 1.30)	1.01 (0.75, 1.34)	0.92 (0.69, 1.22)	0.98	0.625
Diabetes	2.03 (1.16, 3.55)	1.93 (1.25, 2.98)	0.82 (0.42, 1.60)	2.76 (1.66, 4.58)	0.01	<.001
Systolic Blood Pressure	1.00 (0.98, 1.01)	1.02 (1.01, 1.03)	1.03 (1.01, 1.04)	1.01 (1.00, 1.03)	0.001	0.007
High Cholesterol	1.30 (0.59, 2.88)	2.48 (1.39, 4.44)	1.89 (0.71, 5.00)	3.52 (1.56, 7.95)	0.437	<.001
Low-density Lipoprotein	1.18 (0.90, 1.54)	0.85 (0.69, 1.05)	1.00 (0.72, 1.38)	1.23 (0.96, 1.57)	0.404	0.013
High-density Lipoprotein	1.23 (0.94, 1.61)	1.08 (0.87, 1.33)	0.85 (0.61, 1.18)	0.98 (0.75, 1.29)	0.065	0.714
24 hour urine protein	0.94 (0.52, 1.72)	0.92 (0.60, 1.41)	1.14 (0.57, 2.27)	0.89 (0.54, 1.48)	0.879	0.889
High Sensitivity CRP	1.06 (0.79, 1.44)	1.26 (0.97, 1.65)	1.08 (0.76, 1.54)	1.53 (1.13, 2.08)	0.883	0.022
Uric Acid	1.03 (0.89, 1.19)	0.97 (0.86, 1.10)	1.09 (0.92, 1.29)	1.08 (0.93, 1.25)	0.618	0.344
Total Plasma Homocysteine	1.00 (0.94, 1.05)	1.03 (0.98, 1.07)	1.09 (1.03, 1.14)	1.07 (1.02, 1.13)	0.001	0.017
Lipoprotein(a)	1.19 (0.92, 1.53)	1.12 (0.97, 1.30)	1.23 (0.89, 1.70)	1.06 (0.90, 1.26)	0.29	0.319
Calcium	0.76 (0.45, 1.30)	0.79 (0.51, 1.20)	1.00 (0.55, 1.83)	0.97 (0.59, 1.58)	0.546	0.494
Phosphate	1.18 (0.89, 1.56)	1.25 (1.00, 1.56)	0.98 (0.69, 1.39)	1.10 (0.84, 1.44)	0.443	0.143
Total Parathyroid Hormone	0.82 (0.54, 1.25)	0.83 (0.58, 1.19)	0.69 (0.42, 1.15)	0.93 (0.62, 1.39)	0.337	0.599

Figure 1: Mean aortic valve calcification by eGFR illustrates the inverse relationship between aortic valve calcification and eGFR. Dashed lines represent 95% confidence intervals.



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