Relation of Aortic Valve Calcium to Chronic Kidney Disease (from the Chronic Renal Insufficiency Cohort Study)

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Although subjects with chronic kidney disease (CKD) are at markedly increased risk for cardiovascular mortality, the relation between CKD and aortic valve calcification has not been fully elucidated. Also, few data are available on the relation of aortic valve calcification and earlier stages of CKD. We sought to assess the relation of aortic valve calcium (AVC) with estimated glomerular filtration rate (eGFR), traditional and novel cardiovascular risk factors, and markers of bone metabolism in the Chronic Renal Insufficiency Cohort (CRIC) Study. All patients who underwent aortic valve scanning in the CRIC study were included. The relation between AVC and eGFR, traditional and novel cardiovascular risk factors, and markers of calcium metabolism were analyzed using both unadjusted and adjusted regression models. A total of 1,964 CRIC participants underwent computed tomography for AVC quantification. Decreased renal function was independently associated with increased levels of AVC (eGFR 47.11, 44.17, and 39 ml/min/1.73 m^2, respectively, $p < 0.001$). This association persisted after adjusting for traditional, but not novel, AVC risk factors. 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 nonblack patients. In conclusion, our study shows that eGFR is associated in a dose-dependent manner with AVC in patients with CKD, and this association is independent of traditional cardiovascular risk factors. **(Am J Cardiol 2015;115:1281−1286)**

Patients with chronic kidney disease (CKD) have increased cardiovascular morbidity and mortablity, and clinical studies indicate that the prevalence and progression of aortic valve calcium (AVC) is increased in patients with end-stage renal disease.[1] The prevalence of AVC in patients with earlier stages of CKD, however, is not known. The Chronic Renal Insufficiency Cohort (CRIC) study is a large, prospective epidemiologic study of patients with varying degree of CKD. All CRIC study participants underwent assessment for AVC by medical history and measurement of calcium on electron beam computed tomography (CT). In this analysis, we examine the relation between impaired renal function and AVC and explore the association of various traditional Framingham risk factors, novel cardiovascular risk factors including inflammatory (C-reactive protein [CRP]) and novel lipid biomarkers (lipoprotein [Lp](a)), and markers of bone metabolism with AVC in patients with CKD.

Methods

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 from May 2003 to August 2008 from 7 clinical centers in the United States.[2] 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 and those on dialysis or recipients of a kidney transplant or those taking immunosuppressant drugs were excluded from study participation. An eGFR entry criterion (20 to 70 ml/min/1.73 m^2) was used as an enrollment criterion to limit the proportion of older subjects who were recruited with age-related diminutions of GFR but otherwise nonprogressive CKD. A total of 3,939 CRIC participants were screened for this analysis. Of those, 2,068 had baseline noncontrast CT scans with AVC quantification and 1,964 had CT scans between their baseline and year 3 visit. These 1,964

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Table 1
Baseline characteristics of study participants by degree of aortic valve calcification. Data was taken from the non-contrast CT visit, if available, or from the initial baseline visit. Data taken at the baseline visit include total metabolic equivalents, phosphate, total parathyroid hormone, lipoprotein(a), plasma homocysteine, high-sensitivity C-reactive protein, and 24-hour albumin

	All with AVC Measured (n=1964)	*AVC and AVRING both =0 (n=1023)*	*AVC + AVRING >0 - 100 (n=515)*	*AVC + AVRING >100 (n=426)*	*p-value*
Participant Age	58.45 (11.45)	53.16 (11.73)	62.26 (7.90)	66.53 (7.00)	<.0001
Female	918 (47%)	466 (46%)	262 (51%)	190 (45%)	0.0864
Male	1046 (53%)	557 (54%)	253 (49%)	236 (55%)	.
Black	672 (34%)	342 (33%)	192 (37%)	138 (32%)	0.2167
Not Black	1292 (66%)	681 (67%)	323 (63%)	288 (68%)	.
Self-reported history of CVD	494 (25%)	169 (17%)	149 (29%)	176 (41%)	<.0001
Current Smoker	194 (10%)	111 (11%)	43 (8%)	40 (9%)	0.2791
Body Mass Index (kg/m-2)	31.13 (6.70)	30.57 (6.87)	31.73 (6.58)	31.72 (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 (MET h/wk)	209.93 (145.91)	228.87 (161.28)	198.37 (125.59)	178.24 (120.95)	<.0001
Diabetes Mellitus	917 (47%)	384 (38%)	281 (55%)	252 (59%)	<.0001
Glucose (mg/dL)	113.80 (47.85)	110.24 (46.95)	118.78 (51.33)	116.36 (44.95)	0.0020
Hemoglobin A1C (%) at Baseline	6.50 (1.52)	6.33 (1.55)	6.73 (1.52)	6.64 (1.36)	<.0001
Systemic Hypertension Diagnosis	1703 (87%)	816 (80%)	478 (93%)	409 (96%)	<.0001
Systolic Blood Pressure (mmHg)	126.59 (21.25)	123.63 (20.35)	127.75 (21.99)	132.28 (21.21)	<.0001
Diastolic Blood Pressure (mmHg)	70.55 (12.45)	73.22 (12.35)	68.64 (12.11)	66.44 (11.57)	<.0001
Pulse Pressure	56.04 (18.56)	50.41 (16.47)	59.10 (18.05)	65.88 (18.99)	<.0001
High Cholesterol Diagnosis	1698 (86%)	834 (82%)	463 (90%)	401 (94%)	<.0001
Low-density Lipoprotein (mg/dL)	103.07 (34.82)	105.58 (34.81)	100.84 (34.99)	99.76 (34.23)	0.0041
High-density Lipoprotein (mg/dL)	48.97 (15.76)	49.27 (16.06)	50.16 (16.99)	46.80 (13.12)	0.0039
Triglycerides (mg/dL)	154.61 (105.91)	155.52 (112.37)	151.24 (97.79)	156.50 (99.39)	0.7003
eGFR using CRIC equation	44.60 (17.58)	47.11 (18.94)	44.18 (16.31)	39.03 (13.97)	<.0001
24H Urine Protein (g/24H)	1.07 (2.16)	1.15 (2.24)	0.94 (2.01)	1.05 (2.16)	0.2369
Median (IQR)	0.17 (0.07 - 0.93)	0.18 (0.07 - 1.02)	0.15 (0.06 - 0.67)	0.18 (0.07 - 0.94)	0.0697
24H Urine Albumin (g/24H)	0.74 (1.76)	0.84 (1.93)	0.60 (1.39)	0.69 (1.74)	0.0481
Median (IQR)	0.05 (0.01 - 0.56)	0.06 (0.01 - 0.65)	0.04 (0.01 - 0.44)	0.05 (0.01 - 0.41)	0.3405
High Sensitivity CRP (mg/dL)	4.64 (7.64)	4.18 (7.28)	4.85 (7.29)	5.48 (8.77)	0.0100
Median (IQR)	2.22 (0.94 - 5.23)	1.94 (0.87 - 4.69)	2.37 (0.96 - 5.97)	2.64 (1.14 - 6.04)	0.0001
Uric Acid (mg/dL)	7.17 (1.88)	7.01 (1.89)	7.21 (1.87)	7.51 (1.85)	<.0001
Total Plasma Homocysteine (umol/L)	14.35 (5.62)	13.54 (5.03)	14.17 (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)	0.5973
Phosphate (mg/dL)	3.70 (0.67)	3.66 (0.68)	3.75 (0.67)	3.73 (0.66)	0.0206
Total Parathyroid Hormone (pg/ml)	69.47 (70.19)	70.12 (68.65)	63.15 (49.15)	75.53 (91.58)	0.0259
Median (IQR)	50.00 ((33.00 - 81.00)	50.00 (32.40 - 80.00)	47.00 (32.90 - 76.50)	54.45 (34.00 - 89.00)	0.0532
Serum 25(OH)-Vitamin D (ng/mL)	26.14 (14.35)	25.93 (14.14)	26.82 (14.85)	25.77 (14.22)	0.6191
Median (IQR)	23.85 (14.30 - 35.50)	23.75 (15.20 - 34.95)	24.50 (14.10 - 36.95)	23.80 (14.00 - 34.60)	0.6654
Lipoprotein(a) (mg/dl)	36.70 (40.73)	34.51 (40.34)	38.65 (40.58)	39.59 (41.64)	0.0452
Median (IQR)	20.70 (7.40 - 54.40)	16.95 (7.10 - 47.80)	23.65 (8.20 - 61.00)	23.00 (7.90 - 61.30)	0.0116

patients were included in the unadjusted analysis, and a subset of those with nonmissing eGFR calculated by the CRIC equation was used for the adjusted analyses (n = 1,923). Data used in the analyses were taken from first noncontrast CT scan visit with the exception of the following variables which were taken from the baseline study visit: total metabolic equivalent (MET sum, MET h/wk), hemoglobin A1c (percentage), 24-hour urine albumin (gram per 24 hours), high-sensitivity CRP, uric acid (milligrams per deciliter), total plasma homocysteine (micromoles per liter), phosphate (milligrams per deciliter), total parathyroid hormone (PTH, picogram per milliliter), and Lp(a) (milligrams per deciliter).

This study was approved by the institutional review boards from each of the participating clinical centers and the scientific and data co-ordinating center. A written informed consent was obtained from all participants. This study also conformed to the Health Insurance Portability and Accountability Act guidelines.

Estimated glomerular filtration rate (eGFR) was computed using the Modification of Diet in Renal Disease Study equation.[3] CKD was defined as an eGFR <60 ml/min/1.73 m^2 based on the National Kidney Foundation's Kidney disease Outcome Quality Initiative guidelines.

All CRIC participants included in this analysis underwent baseline noncontrast CT scans, which were analyzed for both coronary artery and AVC. Spatial resolution for each system was 1.15 mm^3 for multidetector detector row CT (0.68 × 0.68 × 2.50 mm) and 1.38 mm^3 for electron beam CT (0.68 × 0.68 × 3.00 mm). Full details concerning the equipment, scanning methods, and CT quality control in CRIC, including results of coronary artery calcium associations with GFR, have been reported previously.[4]