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Cross-Sectional Association of Kidney Function with Valvular and Annular Calcification: The Framingham Heart Study

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Valvular calcification is common in the setting of end-stage kidney disease and is associated with increased risks for cardiovascular disease events. It is unknown whether the prevalence of valvular calcification is increased in milder kidney disease after accounting for cardiovascular risk factors. Participants who attended the sixth examination of the Framingham Offspring Study (1995 to 1998) were eligible. Kidney function was estimated by GFR using the simplified Modification of Diet in Renal Disease Study equation. Mitral annular calcification (MAC), aortic sclerosis, and aortic annular calcification were assessed by two-dimensional echocardiography. Logistic regression was used to examine the odds of valvular calcification among participants with chronic kidney disease (CKD; GFR < 60 ml/min per 1.73 m²). A total of 3047 participants (52% women; mean age 59 ± 10 yr) were available for analysis. CKD was present in 8.6% (*n* = 262) of the sample. Among participants with valve/annular calcification (*n* = 284; 9.3%), 20% had CKD, compared with 7% in patients without valvular calcification. After adjustment for age, gender, systolic and diastolic BP, hypertension treatment, total/HDL cholesterol, body mass index, diabetes, smoking status, and cardiovascular disease, participants with CKD had a 60% increased odds of MAC (odds ratio 1.6; 95% confidence interval 1.03 to 2.5). There was no significant association between CKD and either aortic sclerosis or aortic annular calcification (odds ratio 1.1 and 1.1, respectively). After age and gender adjustment, the combination of both CKD and MAC was associated with a three-fold increased risk for death compared with those with neither condition (*P* = 0.0004). In the community, CKD is associated with presence of MAC before the onset of ESRD. Further research is warranted to understand whether traditional and novel vascular risk factor burden, as well as metabolic derangements found in early kidney disease, can account for the CKD–MAC association.

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Chronic kidney disease (CKD) is a risk factor for cardiovascular disease (1–3) and is associated with increased all-cause mortality (2–4). The increased risks are evident at even moderate reductions in kidney function (1–4).

As compared with patients without, patients who have ESRD and are receiving renal replacement therapy have a higher prevalence of valvular calcification, including mitral annular calcification (MAC) (5–10), and aortic calcification (7–10). Valvular calcification among dialysis patients is associated with subclinical measures of atherosclerosis (11) and is a powerful predictor of cardiovascular disease events (10,12) and all-cause mortality (8,10).

We and others have shown previously that MAC predicts atrial fibrillation (13,14), stroke (15,16), and cardiovascular disease morbidity and mortality (17,18). Aortic valve sclerosis also is associated with increased cardiovascular disease morbidity and mortality (19). Because CKD increases both cardiovascular risk (1–4) and valve calcification (5–10), it is plausible that one of the mechanisms by which CKD increases cardiovascular risk is *via* valve calcification.

We hypothesized that MAC, aortic sclerosis, and aortic annular calcification would be associated with CKD, adjusting for coexistent cardiovascular disease risk factors. The Framingham Heart Study, a prospective cohort study, offers an opportunity to examine the cross-sectional relations between kidney function and valvular calcification in the community.

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Materials and Methods

Study Sample

The Framingham Heart Study began in 1948 with the enrollment of 5209 men and women (20,21). In 1971, 5124 men and women were

enrolled into the Framingham Offspring Study, which included the children (and their spouses) of the original cohort. Offspring participants underwent examinations approximately every 4 yr; the design and methods have been described previously (22,23). The sample in our study was composed of Framingham Offspring Study participants who attended the sixth examination cycle between 1995 and 1998. Of 3532 participants who attended the index examination, 118 were excluded because of missing covariate information; 22 were excluded because of missing creatinine data; 67 were excluded because of unavailable echocardiograms; and 30, 264, and 24 participants had missing MAC, aortic sclerosis data, and aortic annular calcification data, respectively. The Framingham Heart Study protocol was approved by the Boston Medical Center Institutional Review Board, and all participants provided written informed consent.

Kidney Function Assessment: Exposures

Kidney function was estimated by GFR, which was calculated using the simplified Modification of Diet in Renal Disease (MDRD) Study equation (24,25), defined as $GFR = 186.3 \times (\text{serum creatinine})^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ for women})$. $GFR > 200 \text{ ml/min per } 1.73 \text{ m}^2$ were set at 200. Our definition of CKD was based on the National Kidney Foundation Kidney Disease Outcomes Quality Initiative working group definition of CKD as a $GFR < 60 \text{ ml/min per } 1.73 \text{ m}^2$ (25). Serum creatinine was measured using the modified Jaffe method. Because creatinine measurements can vary across different laboratories, creatinine was calibrated using a two-step process. First, Third National Health and Nutrition Examination Survey serum creatinine values were calibrated to the Cleveland Clinic Laboratory, requiring a correction factor of 0.23 mg/dl (26). Subsequently, mean serum creatinine values from Framingham, by gender-specific age groups (20 to 39, 40 to 59, 60 to 69, and 70+), were aligned with the corresponding corrected Third National Health and Nutrition Examination Survey age- and gender-specific means (27).

Risk Factor Assessment: Confounders

Details regarding the methods of routine risk factor measurement and laboratory analysis at the Framingham Heart Study examinations have been described (28). Participants who had fasting glucose level $\geq 126 \text{ mg/dl}$ (7.0 mmol/L) and/or were receiving oral hypoglycemic or insulin treatment were defined as having diabetes. Hypertension was defined as systolic BP $\geq 140 \text{ mmHg}$ or diastolic BP $\geq 90 \text{ mmHg}$ (average of two readings taken by the examining physician) or receiving medication for treatment of hypertension. Fasting lipid measures included total and HDL cholesterol. Smoking status was defined as smoking in the year preceding the examination. Body mass index (BMI) was defined as weight divided by height squared (kg/m^2).

Echocardiographic Measurements: Dependent Variables

Participants received routine echocardiography with a Hewlett Packard Sonos 1000 ultrasound machine and 2.5-MHz transducer. Echocardiograms were interpreted blinded to clinical data. Moderate to severe MAC was considered present when an echo-dense band was visualized in the region of the mitral annulus that was $>0.3 \text{ cm}$ thick on the M-mode or when the two-dimensional study demonstrated calcification of more than one third of the circumference of the annulus in the parasternal short-axis view. Participants were considered to have moderate or severe aortic sclerosis when the aortic cusps had diffuse thickening. Moderate or severe aortic annular calcification was considered present when more than one half of the aortic annulus demonstrated increased echogenicity and appeared thickened. For all determinations

of valvular calcification, interpreters confirmed visualization in more than one view.

Statistical Analyses

Baseline characteristics were examined by presence or absence of valvular/annular calcification. Valvular and annular calcification of both the aortic and the mitral valves was combined into one composite phenotype of “at least one” affected valve/annulus because of the assumed shared pathogenesis and shared atherosclerotic risk factors (29). Logistic regression models (30) using SAS (31) were constructed to examine whether CKD was associated with MAC, aortic sclerosis, or aortic annular calcification. There was no significant gender-CKD interaction for valvular/annular calcification; therefore, all analyses were performed gender pooled. Covariates in the multivariable-adjusted model included age, gender, systolic and diastolic BP, hypertension treatment, total/HDL cholesterol, BMI, diabetes, smoking, and prevalent cardiovascular disease. Aortic stenosis was not included as a dependent variable because there were too few cases ($n = 55$) for meaningful analysis. Secondary analyses in which participants with severe kidney disease ($GFR < 15 \text{ ml/min per } 1.73 \text{ m}^2$) were excluded ($n = 2$) were performed. To examine the association between kidney disease and valve calcium independent of pre-existing heart disease, we performed secondary analyses after excluding participants with prevalent myocardial infarction or congestive heart failure ($n = 149$). We also examined whether GFR as a continuous variable was associated with valvular/annular calcification.

In descriptive secondary analyses, we used age- and gender-adjusted Cox proportional hazards models to examine the risk for death through December 31, 2004, among those with neither CKD nor MAC, CKD but no MAC, MAC but no CKD, or both MAC and CKD. For all analyses, a two-sided $P < 0.05$ was considered statistically significant.

Results

Participant Characteristics

Overall, 3047 participants (52% women; mean age $59 \pm 10 \text{ yr}$) were available for analysis, 8.6% ($n = 262$) of whom had CKD (defined as $GFR < 60 \text{ ml/min per } 1.73 \text{ m}^2$). Among the participants with CKD, 180 had $GFR > 50$, 54 had GFR 40 to 50, 19 had GFR 30 to 40, six had GFR 20 to 30, and three had GFR 10 to 20. A total of 284 (9.3%) participants had at least one moderate or severely calcified valve, composed of 130 cases of MAC, 188 cases of aortic sclerosis, and 112 cases of aortic annular calcification. The prevalence of valve disease by CKD status is displayed in Figure 1. Participants with valve calcification were older; less likely to be female; and more likely to have hypertension, diabetes, and higher mean total/HDL cholesterol ratio and mean BMI (Table 1). Mean GFR values were significantly lower among participants with valvular calcification ($P < 0.001$). Among participants with at least one calcified valve, 20% had CKD, compared with 7% of participants without significant valve calcification.

Participants with CKD were 1.9 times more likely to have MAC compared with participants without CKD (Table 2, age- and gender-adjusted comparisons). After multivariable adjustment for cardiovascular disease and its risk factors, the odds of MAC were 60% higher among participants with CKD as compared with those without. Participants with CKD were nearly 1.3 times more likely to have aortic sclerosis or aortic annular calcification, but these relations were NS in age- and gender-

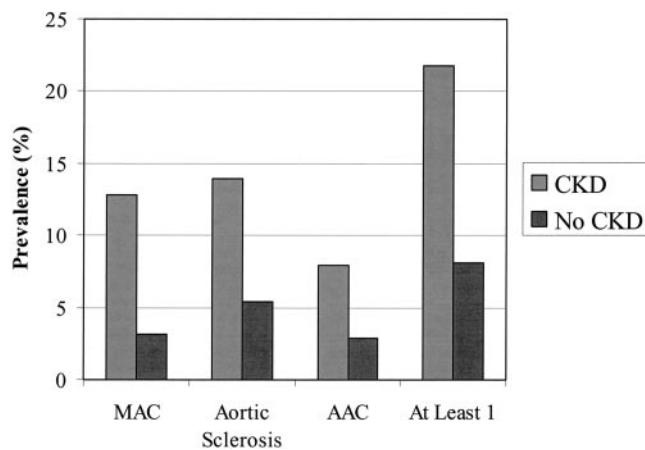


Figure 1. Prevalence of mitral annular calcification (MAC), aortic sclerosis, aortic annular calcification, or at least one calcified valve by the presence or absence of kidney disease (defined as GFR < 60 ml/min per 1.73 m²). AAC, aortic annular calcification. *P* values for the age- and gender-adjusted and multivariable analyses can be found in Table 2.

adjusted analyses (Table 2). Participants with CKD were 1.5 times more likely to have at least one calcified valve/annulus. The relation between CKD and significant valve/annular calcification persisted after adjustment for age and gender but was no longer significant after multivariable adjustment (Table 2).

In secondary analyses, the results were essentially unchanged after exclusion of participants with GFR < 15 ml/min per 1.73 m² from the analysis (*n* = 2) or those with prevalent myocardial infarction or congestive heart failure: Odds ratios for MAC, aortic sclerosis, aortic annular calcification, or at least one calcified valve were 1.9, 1.3, 1.1, and 1.4, respectively. Examining GFR as a continuous variable, the fully adjusted odds of MAC, aortic sclerosis, aortic annular calcification, or at least one affected valve were 1.2, 1.1, 1.1, and 1.1, respectively, per SD decline in GFR (25 ml/min per 1.73 m²; Table 2); all 95% confidence intervals included 1.0.

Relation among CKD, MAC, and All-Cause Mortality

In a secondary analysis, we examined mortality by CKD and MAC status. Overall, there were 195 deaths. Compared with those without CKD or MAC (*n* = 2691), after adjustment for age and gender, those with CKD but no MAC (*n* = 226) had an 1.8-fold increased risk for death (*P* = 0.004), those with MAC but no CKD (*n* = 94) had a 2.5-fold increased risk for death (*P* = 0.0004), and those with both CKD and MAC (*n* = 36) had a 3.0-fold increased risk for death (*P* = 0.0004; Figure 2).

Discussion

In our community-based sample, valvular calcification was more prevalent among individuals with CKD. Overall, participants with kidney disease were 50% more likely to have at least one calcified valve/annulus. The relation between CKD and significant valvular calcification was markedly attenuated by adjustment for cardiovascular risk factors and disease, suggesting that shared vascular disease risk factors partially me-

diate the increased prevalence of valvular calcification in the setting of CKD. However, CKD conferred a 60% increased odds of mitral annular calcification after multivariable adjustment.

To our knowledge, these data are the first to demonstrate an association between CKD and MAC in an unselected community-based sample after adjustment for shared risk factors. A previous study from the Jackson cohort of the ARIC Study noted an unadjusted association between elevated serum creatinine and MAC (32); however, the data were not adjusted for age, gender, cardiovascular disease, or vascular risk factors. Indeed, MAC has been reported to be more prevalent among patients who were on dialysis (5–10), but our data suggest that this relation precedes the onset of ESRD.

The cause of the association between CKD and MAC is unclear but may stem from underlying vascular and metabolic derangements that are found in kidney disease. In previous work, we showed that MAC is associated with increased cardiovascular disease risk (17). In that article, we hypothesized that the increased risk for cardiovascular disease might be due to shared risk factors, with the mitral valve annulus functioning as an integrator of cardiovascular disease risk factor burden. Individuals with CKD are known to have a higher prevalence of traditional cardiovascular disease risk factors (33). A recent study of 92 dialysis patients demonstrated associations among valvular calcification, inflammation, and subclinical atherosclerosis among participants without clinical cardiovascular disease (11), suggesting that valvular calcification is a good marker of underlying atherosclerotic burden.

It is unclear why we found significant results for MAC only and not for aortic sclerosis or aortic annular calcification. Power calculations, constructed for an α of 0.05 and an odds ratio of 2, demonstrate reasonable power (power of 0.75 for MAC) to excellent power (power of 0.94 for at least one calcified valve) for detection, with the exception of aortic annular calcification (power of 0.69). We acknowledge that our statistical power was such that we may have failed to detect modest associations between CKD and aortic annular calcification or aortic sclerosis. Similar findings of strong associations between biochemical derangements and mitral but not aortic calcification in dialysis patients have been observed in another study (9). Further basic and clinical research is necessary to elucidate these issues better.

Individuals with CKD have a high prevalence of novel cardiovascular disease risk factors, including increased levels of apolipoprotein A1, homocysteine, lipoprotein(a), fibrinogen, and C-reactive protein (34). Markers of inflammation and thrombosis, including C-reactive protein, fibrinogen, factor VII, and albumin, are associated with worsening of kidney function (35). CKD is also associated with anemia (36), and individuals with both CKD and anemia are at a nearly three-fold increased risk for cardiovascular disease (37). Thus, it is possible that the high prevalence of novel risk factors in CKD also contributes to the observed increased odds of MAC.

Milder versions of metabolic derangements that are observed in hemodialysis patients may also contribute to the increased prevalence of MAC in our study sample. The calcium-phosphorous product is higher in patients with, as compared with

Table 1. Characteristics of participants with and without significant valvular calcification^a

	No Significant Valvular/ Annular Calcification (<i>n</i> = 2763)	At Least One Calcified Valve/Annulus ^b (<i>n</i> = 284)
Age (yr)	58 ± 10	67 ± 8 ^d
Gender (% female)	54	36 ^d
Systolic BP (mmHg)	127 ± 19	134 ± 20
Diastolic BP (mmHg)	74 ± 10	71 ± 10
Hypertension (%)	43	67 ^e
Total/HDL cholesterol	4.3 ± 1.5	4.8 ± 1.8 ^e
Diabetes (%)	10	21 ^f
BMI (kg/m ²)	27.7 ± 4.9	29.2 ± 5.2 ^d
Current smoking (%)	14	14
Prevalent cardiovascular disease (%)	11	42 ^d
Creatinine (mg/dl)	0.9 ± 0.2	1.0 ± 0.4 ^d
GFR (ml/min per 1.73 m ²)	89 ± 25	78 ± 25 ^d
CKD ^c (%)	7	20 ^f

^aPrevalent cardiovascular disease defined as recognized myocardial infarction or heart failure. BMI, body mass index; CKD, chronic kidney disease.

^bIncludes 130 cases of mitral annular calcification (MAC), 112 cases of aortic annular calcification, and 188 cases of aortic sclerosis.

^cCKD denotes GFR < 60 ml/min per 1.73 m².

^d*P* < 0.001, ^e*P* < 0.01, ^f*P* < 0.05, for age- and gender-adjusted comparison.

Table 2. Odds of valvular calcification in participants with and without chronic kidney disease^a

	By Presence/ Absence of CKD		Per SD Decrease in GFR	
	OR	95% CI	OR	95% CI
MAC (<i>n</i> = 130)				
age and gender adjusted	1.9	1.3 to 3.0 ^c	1.2	1.0 to 1.6
multivariable adjusted ^b	1.6	1.03 to 2.5 ^d	1.2	1.0 to 1.5
Aortic sclerosis (<i>n</i> = 188)				
age and gender adjusted	1.3	0.8 to 2.0	1.1	0.9 to 1.3
multivariable adjusted ^b	1.1	0.7 to 1.7	1.1	0.9 to 1.4
Aortic annular calcification (<i>n</i> = 112)				
age and gender adjusted	1.3	0.8 to 2.2	1.2	0.9 to 1.5
multivariable adjusted ^b	1.1	0.7 to 1.9	1.1	0.9 to 1.4
At least one calcified valve (<i>n</i> = 284)				
age and gender adjusted	1.5	1.1 to 2.2 ^d	1.1	0.9 to 1.3
multivariable adjusted ^b	1.3	0.9 to 1.9	1.1	1.0 to 1.3

^aOR, odds ratio; CI, confidence interval.

^bAdjusted for age, gender, systolic and diastolic BP, hypertension treatment, total/HDL cholesterol, BMI, diabetes, cardiovascular disease, and smoking.

^c*P* < 0.01.

^d*P* < 0.05.

patients without, mitral valve calcium; no difference was seen among patients with and without aortic valve calcium (9). Among peritoneal dialysis patients, patients with valve calcium had higher levels of serum calcium, phosphate, and parathyroid hormone (8). Elevated serum phosphate level is associated with an increased risk for valvular procedures in hemodialysis patients, highlighting the clinical ramifications of calcium-

phosphorus derangements as well (38). Less is known regarding the relation of predialysis, valvular calcification, and biochemical abnormalities. However, significant biochemical abnormalities do exist early in kidney disease. Among predialysis patients, parathyroid hormone begins to rise as the creatinine clearance approaches 60 ml/min (39). In addition, serum phosphorous levels and calcium-phosphorous products

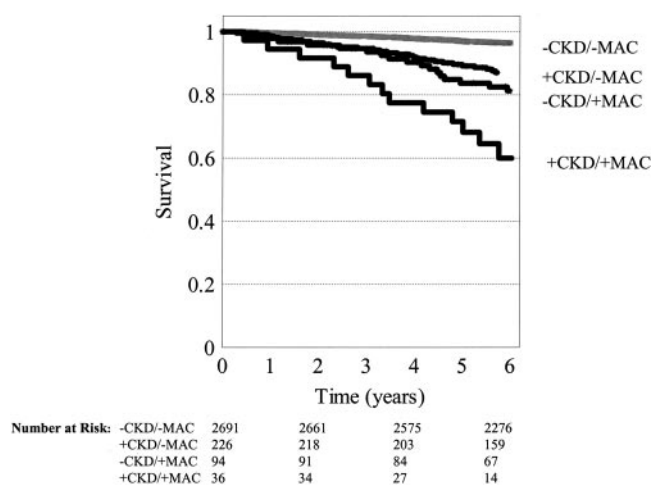


Figure 2. Kaplan-Meier curves for those without chronic kidney disease (CKD) or MAC, CKD but no MAC, MAC but no CKD, and both CKD and MAC.

are elevated in predialysis patients (25), and levels of 1,25 vitamin D are decreased (40), suggesting potential mechanisms for our findings.

Biomarkers of calcium-regulatory proteins may be involved in the pathogenesis of extra-osseous calcification in dialysis patients (41). Fetuin-A (α 2-Heremans-Schmid glycoprotein), an inhibitor of calcium \times phosphate precipitation, has been shown to be lower in dialysis patients as compared with healthy control subjects (42) and is associated with coronary calcium (43). Matrix Gla protein, which has been shown to be correlated inversely with coronary artery calcification (44), has been hypothesized to act similarly in dialysis patients. Thus, it is possible that similar metabolic derangements occur among individuals with moderate degrees of CKD as well, predisposing these individuals to valvular calcification.

In analyses that examined GFR as a continuous (*versus* categorical) variable, the association with MAC was no longer significant. Whereas the lack of association between GFR and MAC in a linear model might be consistent with a threshold effect, we were underpowered to establish a threshold effect. Another explanation for our negative findings in the continuous model may be related to potential misclassification of GFR estimation derived from use of the MDRD equation in samples that were free of kidney disease. The MDRD equation has been validated in patients with GFR < 90 ml/min per 1.73 m²; values outside this range are extrapolated (45). A recent study showed that the MDRD equation underestimates GFR by 29% in healthy individuals but only by 6.2% among patients with CKD (46). Our definition of CKD as a disease trait (GFR < 60 ml/min per 1.73 m²) falls within the range that the MDRD equation has been validated (24), improving the robustness of our results for our dichotomous analysis.

Limitations

Our ascertainment of kidney disease by a single serum creatinine measure may have led to misclassification as it was not possible to determine whether participants fulfilled criteria for

kidney disease for at least a 3-mo period. We performed a statistical but not biochemical calibration of our serum creatinine data to the Cleveland Clinical laboratory. Nonetheless, this approach is considered the standard in epidemiologic studies. Our study sample was not nationally representative or ethnically diverse. Nevertheless, the relations of risk factors to coronary heart disease outcomes observed in Framingham recently have been validated in six ethnically and geographically diverse cohorts, and they were found to be applicable in other populations (47,48). We did not adjust for multiple testing, and it may be argued that a lower *P* value threshold could be used to indicate statistical significance. We submit that the biologic plausibility of the observed association suggests that our results were not simply the result of multiple testing. However, we acknowledge that it is important to validate our findings in other cohorts. Our data were cross-sectional, and we could not determine the temporal and causal relations among cardiovascular disease risk factors, CKD, and valvular calcification. Prospective studies will be necessary to help to elucidate these relations. We assessed only moderate or greater MAC, aortic sclerosis, and aortic annular calcification. Thus, our results may not be comparable directly to other studies that included milder degrees of valvular calcification. Last, we did not have measures of biochemical data, such as calcium, phosphorous, and parathyroid hormone.

Clinical and Research Implications

The cause of the increased risk for vascular disease among individuals with CKD is not fully understood. Further research is warranted to determine whether traditional and novel vascular risk factor burden, as well as metabolic derangements that are found in early kidney disease, accounts for this association. Whether MAC is a causal mechanism that mediates this association or a risk marker remains to be determined. Such research may uncover pathophysiologic mechanisms that are implicated in the increased cardiovascular disease risk seen in CKD.

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