Prevalence and Prognostic Implications of Mitral and Aortic Valve Calcium in Patients With Chronic Kidney Disease

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Calcium in the cardiac valves can be observed in patients with severe chronic kidney disease (CKD). However, the prevalence and prognostic implications of left-sided cardiac valve calcium in patients with stage 2 and 3 CKD (estimated glomerular filtration rate (eGFR) of 60 to 89 and 30 to 59 ml/min/1.73 m^2 respectively) is unknown. The present study investigates the prevalence of mitral and aortic valve calcium in patients with stage 2 and 3 CKD and evaluates its association with all-cause mortality. In patients with stage 2 and 3 CKD who underwent clinically indicated coronary computed tomography angiography, the presence of mitral and/or aortic valve calcium was assessed. Patients were divided into 2 groups according to the presence of mitral and/or aortic valve calcium on coronary computed tomography angiography. Patients were followed for the occurrence of all-cause mortality (primary end point). Of 204 stage 2 and 3 CKD patients (54% men, mean age 60 ± 10 years), 66 (32%) patients had mitral and/or aortic valve calcium. During a median follow-up of 6 years (IQR; 2, 9 years), 29 (14%) patients died. Patients with mitral and/or aortic valve calcium showed significantly higher mortality rates compared with patients without left-sided valve calcium (log-rank p = 0.009). Mitral valve calcium was independently associated with increased risk of all-cause mortality, whereas aortic valve calcium was not. In conclusion, the prevalence of left-sided valve calcium in patients with stage 2 and 3 CKD is high. Mitral valve calcium was independently associated with increased risk of all-cause mortality, whereas aortic valve calcium was not. **(Am J Cardiol 2018;122:1732−1737)**

Patients with chronic kidney disease (CKD) exhibit an increased risk of cardiovascular morbidity and mortality.[1] Valvular heart disease is one of the contributors to these increased morbidity and mortality risks.[2] In CKD patients, valvular calcium is an important underlying mechanism of valve dysfunction.[3] Hypertension, inflammation, and dysregulated metabolic pathways, such as disorders in the calcium-phosphate metabolism, lead to the development of valvular calcium in patients with CKD.[4,5] Valvular calcium is associated with an increased risk of all-cause mortality in patients with end-stage renal disease.[6,7] However, the prognostic implications of left-sided valve calcium in patients with stage 2 and 3 CKD (estimated glomerular filtration rate [eGFR] of 60 to 89 ml/min/1.73 m^2 and 30 to 59 ml/min/1.73 m^2 respectively) are unknown. Therefore the aim of the present study was to investigate the prevalence of mitral and aortic valve calcium in patients with stage 2 and 3 CKD who underwent coronary computed tomography angiography (CTA) and to evaluate its association with all-cause mortality.

Methods

Coronary CTA data clinically acquired in patients with stage 2 and 3 CKD between 2005 and 2011 at the Leiden University Medical Centre were retrospectively analyzed. Patients were diagnosed with stage 2 and 3 CKD according to the 2012 Clinical Practice Guideline for the evaluation and Management of CKD, Kidney Disease: Improving Global Outcomes (KDIGO).[8] The clinical indications for coronary CTA were: screening for corornary artery disease (CAD), chest pain, pulmonary vein isolation and ventricular tachycardia ablation. Patients who underwent coronary CTA for screening of transcatheter aortic valve implantation, who underwent mitral and/or aortic valve replacement or repair before index coronary CTA, who were younger than 18 years old and patients with complex congenital heart disease were excluded. Clinical data were collected through review of the electronical medical records (HiX; ChipSoft, Amsterdam, The Netherlands) and the departmental cardiology information system (EPD-vision; Leiden University Medical Centre, Leiden, The Netherlands) and retrospectively analyzed. Estimated glomerular filtration rate was calculated by the Modified Diet in Renal Disease equation.[9] Patients were followed for the

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occurrence of all-cause mortality through case record review and the national death registry. The occurrence of surgical or transcatheter mitral or aortic valve replacement or repair during follow-up was registered through case record review. For retrospective analysis of clinically acquired data, anonymously handled, the institutional review board approved the study and waived the need for patient written informed consent.

Patients were scanned using a 64-slice multidetector row computed tomography (CT) scanner (Aquilion 64, Toshiba Medical Systems, Japan) or a 320-slice CT scanner (Toshiba Multi-slice Aquilion ONE system, Toshiba Medical Systems, Japan). Heart rate and blood pressure were monitored before coronary CTA data acquisition. A noncontrast CT scan was performed for coronary artery calcification burden quantification, followed by contrast coronary CTA for evaluation of obstructive coronary artery disease .[10] Commercially available, post-processing software was used for data analysis (Vitrea FX 6.5; Vital Images, Minnetonka, Minnesota). Calcium burden of the mitral and aortic valve was quantified using the Agatston algorithm on the noncontrast CT scans.[11,12] The calcium of the mitral valve included the mitral annulus and leaflets (this was compared with the contrast CT scans to ensure appropriate quantification of the Agatston score). Coronary anatomy was assessed systematically according to a 17-segment coronary tree model.[13] Obstructive CAD was defined as $\geq 50\%$ stenosis in a coronary artery. Patients were divided into two groups according to the existence of mitral and/or aortic valve calcium. Examples of patients at different CKD stages with or without mitral or aortic valve calcium are demonstrated in Figures 1 and 2.

Continuous variables are reported as median and interquartile range or mean $\pm$ standard deviation, as appropriate. Categorical variables are reported as numbers and percentages. Continuous variables were compared between the groups using the Student's *t*-test or Mann-Whitney *U* test, as appropriate. Categorical variables were compared between the groups using the chi-square test. The Kaplan-Meier method was used to calculate the cumulative event-free survival rates for all-cause mortality from the time of coronary CTA acquisition. The log-rank test was used to compare the cumulative event-free survival rates between groups. Univariable and multivariable Cox proportional

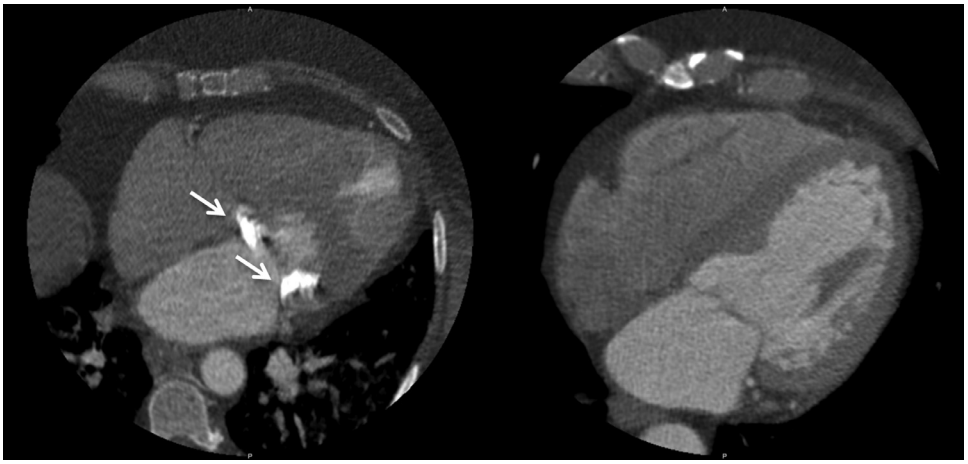

Figure 1. Coronary computed tomography angiography images in a patient with stage 3 chronic kidney disease and significant mitral valve calcium *(left panel, arrows)* and in a patient with stage 2 chronic kidney disease and no mitral valve calcium *(right panel)*.

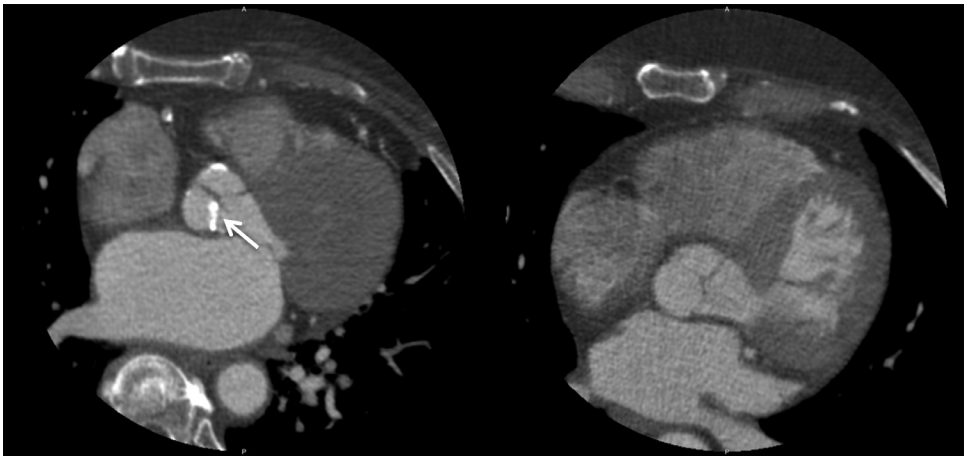

Figure 2. Coronary computed tomography angiography images in a patient with stage 3 chronic kidney disease and significant aortic valve calcium *(left panel, arrow)* and in a patient with stage 2 chronic kidney disease and no aortic valve calcium *(right panel)*.

hazard models were used to evaluate the independent association between mitral or aortic valve calcium with all-cause mortality. The occurrence of surgical or transcatheter mitral or aortic valve replacement or repair during follow-up was introduced as a time-dependent covariate. All analyses were performed with the use of the SPSS software (Version 20.0. Armonk, NY: IBM Corp). A two-sided p value < 0.05 was considered statistically significant.

Results

Of 204 stage 2 and 3 CKD patients (54% men, mean age 60 ± 10 years), 66 (32%) patients had mitral and/or aortic valve calcium. More specifically, 15 (23%) patients had both mitral and aortic valve calcium, 42 (64%) patients had only aortic valve calcium and 9 (14%) patients had only mitral valve calcium. Patients with mitral and/or aortic valve calcium were older, had higher body mass index and more obstructive CAD on coronary CTA compared with patients without left-sided valve calcium (Table 1). CKD stage was not significantly different between patients with or without aortic valve calcium; however in patients with mitral valve calcium, stage 3 CKD was more frequent compared with patients without mitral valve calcium (15 patients (63%) versus 65 patients (36%) respectively, p = 0.013).

A total of 13 patients underwent surgical or transcatheter mitral or aortic valve replacement or repair after the index coronary CTA. During a median follow-up of 6 years (interquartile range 2 to 9 years), 29 (14%) patients died. The total follow-up time was 12 years. The Kaplan-Meier survival curves for patients with and without mitral and/or aortic valve calcium are presented in Figure 3. At univariable analysis, age, CKD stage, body mass index, atrial fibrillation, previous myocardial infarction, and mitral and aortic valve calcium were associated with all-cause mortality (Table 2). At multivariable analysis, mitral valve calcium (introduced as categorical variable) was independently associated with increased risk of all-cause mortality after correcting for age, gender, CKD stage, previous myocardial infarction, atrial fibrillation, and surgical or transcatheter valve replacement or repair, whereas aortic valve calcium was not (Table 3). When the analysis was performed introducing mitral valve calcium and aortic valve calcium as continuous variables, the results did not change and increasing values of mitral valve calcium Agatston scores were independently associated with all-cause mortality whereas aortic valve calcium score was not.

Discussion

In the present study, one-third of patients with stage 2 and 3 CKD had mitral and/or aortic valve calcium. The presence of mitral and/or aortic valve calcium was associated with poor survival in this population, but only mitral valve calcium was independently associated with increased risk of all-cause mortality, whereas aortic valve calcium was not.

The prevalence of valve calcium is high in patients with end-stage renal disease.[6,7,14] However the prevalence of left-sided valve calcium in patients with milder CKD is less well established.[15–17] Among 262 patients with CKD (defined as eGFR <60 ml/min/1.73 m^2) 22% had mitral and/or aortic valve calcium.[16] In addition, in 710 patients with CKD stage 3A (eGFR 45-60 ml/min/1.73 m^2), 80% had one or more left-sided valves with calcium, whereas in 214 patients with CKD stage 3B-5 (eGFR <45 ml/min/1.73 m^2), 88% had one or

Table 1
Baseline characteristics of chronic kidney disease patients with and without mitral and/or aortic valve calcium

Mitral and/or aortic valve calcium			
Variable	No (n = 138)	Yes (n = 66)	p value
Age (years)	58 ± 10	65 ± 8	<0.001
Men	73 (53%)	37 (56%)	0.672
Stage 3 CKD	51 (37%)	29 (44%)	0.339
eGFR MDRD (ml/min/1.73 m^2)	70 (58-80)	61 (53-79)	0.148
Body mass index (kg/m^2)	27 ± 5	29 ± 6	0.035
Smoker	15 (11%)	9 (14%)	0.566
Diabetes mellitus	35 (25%)	22 (33%)	0.235
Hypertension*	78 (57%)	41 (62%)	0.448
Hypercholesterolemia†	51 (37%)	26 (39%)	0.737
Peripheral artery disease	4 (3%)	3 (5%)	0.552
Previous myocardial infarction	13 (9%)	9 (14%)	0.364
Previous CABG/PCI	14 (10%)	10 (15%)	0.299
Previous stroke	5 (4%)	1 (2%)	0.400
Atrial fibrillation	42 (31%)	22 (33%)	0.725
Coronary artery disease on coronary computed tomography angiography			0.044
None	15 (11%)	4 (6%)	
Nonobstructive	74 (55%)	28 (42%)	
Obstructive	45 (34%)	34 (52%)	

CABG = coronary artery bypass grafting; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; MDRD = modification of diet in renal disease; PCI = percutaneous coronary intervention.

* Defined as systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg and/or the use of antihypertensive medication.

† Defined as serum total cholesterol ≥ 230 mg/dl and/or serum triglycerides ≥ 200 mg/dl and/or treatment with lipid lowering drugs.Continuous data are presented as mean ± SD or median (interquartile range). Categorical data are presented as numbers and percentages.

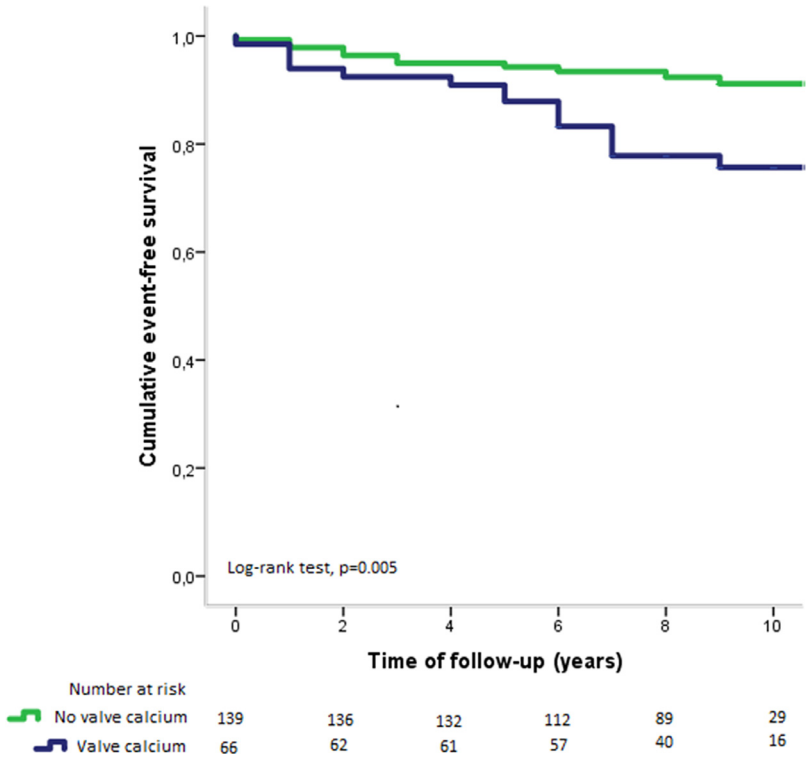

Figure 3. Kaplan-Meier curves with the cumulative event-free survival of stage 2 and 3 chronic kidney disease patients with mitral and/or aortic valve calcium (blue) and patients without (green). (Color version of figure is available online).

Table 2
Univariate cox proportional hazard model demonstrating the association between clinical and computed tomography scan variables and all-cause mortality

Variable	Univariate OR (95% CI)	p value
Age	1.07 (1.03-1.11)	0.001
Male gender	2.00 (0.93-4.31)	0.077
Stage 3 CKD (vs stage 2 CKD)	2.64 (1.23-5.70)	0.013
Coronary artery disease (vs normal)		
Non-obstructive	0.55 (0.15-1.98)	0.356
Obstructive	0.997 (0.29-3.43)	0.997
Body mass index (kg/m^2)	1.08 (1.02-1.14)	0.009
Atrial fibrillation	2.37 (1.12-5.05)	0.025
Peripheral artery disease	8.29 (2.77-24.79)	<0.001
Previous myocardial infarction	3.91 (1.73-8.85)	0.001
Previous stroke	1.13 (0.15-8.31)	0.905
Surgical or transcatheter valve replacement or repair	6.10 (0.81-45.82)	0.079
Mitral valve calcium	2.93 (1.33-6.46)	0.008
Aortic valve calcium	2.18 (1.05-4.52)	0.036

CI = confidence interval; CKD = chronic kidney disease; OR = odds ratio.

more left-sided valves with calcium.[15] The different imaging techniques to analyze left-sided valve calcium (coronary CTA vs echocardiography) and differences in patient characteristics (age, ethnicity and CKD stage and risk factors) in the above-mentioned studies have contributed to the differences in the reported prevalence. Several risk factors for valvular calcium have been proposed in patients with CKD.[4,18] Among 2,070 patients with stage 2 and 3 CKD, 16% had mitral annular calcification.[4] Age, Caucasian race, decreased eGFR and elevated phosphate were independently associated with the presence of mitral annular calcification.[4] Elevated phosphate stimulates secondary hyperparathyroidism and is associated with increased circulating calcium and increased risk of valvular calcium.[4,18] In 92 long-term hemodialysis patients, hypertension, age, and calcium phosphate product were associated with mitral and/or aortic valve calcium.[5]

In the current study, mitral valve calcium was associated with worse CKD stage, whereas aortic valve calcium was not. Asselbergs et al and Fox et al reported similar findings and suggested that disorders in the calcium-phosphate metabolism may cause mitral valve calcium, while aortic valve calcium may be more a degenerative disease.[15,16] In a recent series of 23,088 patients with CKD (eGFR <60 ml/min/1.73 m^2), left-sided valvular heart disease (mitral regurgitation and aortic stenosis) was independently associated with CKD.[2] Furthermore the prevalence of at least mild mitral regurgitation was

Table 3
Multivariable Cox proportional hazard model evaluating the association between mitral and aortic valve calcium and all-cause mortality

	Mitral valve calcium OR (95% CI)	p value	Aortic valve calcium OR (95% CI)	P value
Not adjusted	2.93 (1.33-6.46)	0.008	2.18 (1.05-4.52)	0.036
Adjusted for age	2.32 (1.04-5.14)	0.039	1.55 (0.74-3.27)	0.245
Adjusted for age, gender, and CKD stage	2.45 (1.06-5.64)	0.035	1.53 (0.73-3.24)	0.263
Adjusted for multiple factors*	2.65 (1.15-6.13)	0.022	0.74 (0.34-1.59)	0.437

* Adjusted for age, gender, chronic kidney disease stage, previous myocardial infarction, atrial fibrillation, surgical, or transcatheter valve replacement or repair.Abbreviations: CKD = chronic kidney disease; CI = confidence interval; OR = odds ratio.

much higher than aortic stenosis (42.9% vs 9.5% respectively), probably indicating the high burden of CKD on the structural changes in the mitral valve apparatus.[2]

Studies evaluating the prognosis of patients with CKD and left-sided valve calcium are limited.[6,16] In 262 patients with CKD (defined as eGFR <60 ml/min/1.73 m^2), mitral annular calcium was associated with a threefold increased risk for death.[16] In addition, in 144 hemodialysis patients mitral and aortic valve calcium was associated with higher mortality rates.[6] However, after adjustment for multiple factors (age, gender, race, diabetes mellitus, atherosclerotic cardiovascular disease and pulse pressure) mitral valve calcium remained associated with all-cause mortality, whereas aortic valve calcium was not.[6] The reasons for this finding may lay on the type of valve dysfunction that the valvular calcium cause. Aortic valve calcium leads more frequently to aortic stenosis, whereas mitral valve calcium may lead to mitral regurgitation. Symptoms caused by severe aortic stenosis can only be relieved by aortic valve replacement whereas in symptomatic severe mitral regurgitation, the use of diuretics may lead to symptom relief and mitral valve intervention may be deferred in patients with CKD. In addition, the diagnosis of severe mitral regurgitation may be challenged by the loading conditions of the patient and the presence of valvular calcium. Accordingly, patients may not be referred for mitral valve intervention and the risk of all-cause mortality may increase. The high mortality risk in patients with CKD and left-sided valve calcium underscores the importance of appropriate treatment of these patients. Future studies are needed to investigate the association between mitral valve calcium and CKD and subsequently potential therapeutic targets to prevent valvular calcium.

The present study has several limitations, including its retrospective design. In addition, only patients with stage 2 and 3 CKD with a clinically indicated coronary CTA were included in the present study, giving a potential selection bias. Furthermore, low eGFR is associated with severe coronary calcification, which may cause blooming artifacts affecting the interpretation of CTA coronary stenosis severity.

The prevalence of left-sided valve calcium in patients with stage 2 and 3 CKD is high and was associated with poor survival. Mitral valve calcium was independently associated with increased risk of all-cause mortality, whereas aortic valve calcium was not.

Disclosures

V. Delgado received speaking fees from Abbott Vascular. The other investigators have no conflicts of interest to declare.

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