All-cause Mortality in Hemodialysis Patients with Heart Valve Calcification

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Summary

Background and objectives Calcification of the mitral and aortic valves is common in dialysis patients (CKD-5D). However, the prognostic significance of valvular calcification (VC) in CKD is not well established.

Design, setting, participants, & measurements 144 adult CKD-5D patients underwent bidimensional echocardiography for qualitative assessment of VC and cardiac computed tomography (CT) for quantification of coronary artery calcium (CAC) and VC. The patients were followed for a median of 5.6 years for mortality from all causes.

Results Overall, 38.2% of patients had mitral VC and 44.4% had aortic VC on echocardiography. Patients with VC were older and less likely to be African American; all other characteristics were similar between groups. The mortality rate of patients with calcification of either valve was higher than for patients without VC. After adjustment for age, gender, race, diabetes mellitus, and history of atherosclerotic disease, only mitral VC remained independently associated with all-cause mortality (hazard ratio [HR], 1.73; 95% confidence interval [CI], 1.03 to 2.91). Patients with calcification of both valves had a two-fold increased risk of death during follow-up compared with patients without VC (HR, 2.16; 95% CI, 1.14 to 4.08). A combined CT score of VC and CAC was strongly associated with all-cause mortality during follow-up (HR for highest *versus* lowest tertile, 2.21; 95% CI, 1.08 to 4.54).

Conclusions VC is associated with a significantly increased risk for all-cause mortality in CKD-5D patients. These findings support the use of echocardiography for risk stratification in CKD-5D as recently suggested in the Kidney Disease Improving Global Outcomes guidelines.

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Introduction

Calcification of the mitral and aortic valves is a frequent finding in dialysis patients (CKD-5D) with a prevalence four to five times higher than in the general population (1). Despite the fact that valvular calcification is believed to share risk factors and pathogenic features in common with the more frequently detected vascular calcification (2), data on the prognostic significance of valvular calcification in CKD-5D patients are limited and far from conclusive. Calcification of the cardiac valves has been associated with a poor prognosis in the general population (3–7) and in a prior publication in CKD-5D patients undergoing peritoneal dialysis (8). However, in a series of patients undergoing hemodialysis (9), the association of valvular calcification with mortality was no longer present after adjustment for confounders. Thus, whether valvular calcification provides useful prognostic information in CKD-5D patients remains to be fully elucidated.

To better understand the relationship between valvular calcification and all-cause mortality, we conducted a prospective cohort study of CKD-5D patients. Specifically, we assessed the association of mitral and aortic valve calcification, separately and together, with all-cause mortality. In addition, we tested the hypothesis that the combined presence of coronary and valvular calcification, an estimate of the total cardiovascular calcification burden, would be associated with mortality in CKD-5D patients.

Materials and Methods

Patient Selection

Between January 2004 and November 2005, prevalent adult hemodialysis patients were recruited from two dialysis centers (Denver, CO and New Orleans, LA). Patients were excluded if they were pregnant, lactating, or planning to become pregnant in the 6 months after entry into the study. A total of 148 patients were enrolled, and all of the imaging and biochemical studies described below were performed within a week of each other. For this analysis, four participants who did not undergo an echocardiogram

were excluded, leaving a final sample size of 144 participants. We calculated the minimal detectable hazard ratio comparing individuals with *versus* without valve calcification using this sample size and the following assumptions: (*1*) two-tailed type I error of 5%; (*2*) an annual event rate of 15%; (*3*) a 1.5-year recruitment period; (*4*) 4.5 years of additional follow-up; and (*5*) 40% of the population having valve calcification. Under these assumptions, we would have 80% statistical power to detect a hazard ratio for all-cause mortality comparing individuals with *versus* without valve calcification of 1.98. The study protocol received institutional review board approval, and all participants provided written informed consent before enrollment into the study.

Data Collection

Using a structured questionnaire, self-reported information was collected on age, gender, race, and cigarette smoking. Medical chart reviews were conducted to determine a history of diabetes mellitus, hypertension, dyslipidemia, atherosclerotic cardiovascular disease (ASCVD), and dialysis vintage. History of ASCVD was a composite measure that included myocardial infarction, angina, and peripheral and cerebrovascular disease.

Procedures used to evaluate patients at study visits have been described in detail previously (10). In brief, height and weight were measured, and body mass index was calculated as weight in kilograms divided by height in meters squared. BP was measured three times, after a 15- to 20-minute rest, using a manual aneroid sphygmomanometer with a 30-second rest between each measurement. Measurements were performed with participants in the supine position using the arm that did not contain an arteriovenous fistula or shunt. Pulse pressure was calculated as the difference between systolic and diastolic pressures. The mean of the three pulse pressures was used in these analyses.

Two-dimensional Echocardiography

All of the studies were performed utilizing a Sequoia 512 (Siemens, Erlangen, Germany) for patients in New Orleans and a Vivid 7 (General Electric, Milwaukee, WI) system for patients in Denver. The presence or absence of aortic and mitral valve calcification, separately, was determined visually and only qualitatively. All of the scans were analyzed independently by one experienced investigator (P.R.).

Electron-Beam Computed Tomography (EBCT)

All computed tomography (CT) procedures were performed on a C-150 scanner (GE-Imatron, South San Francisco, CA) with a 100-ms scanning time and a single-slice thickness of 3 mm. Details on the method have been published elsewhere (11). Briefly, a total of 36 to 40 tomographic slices were obtained for each subject during a single breath-holding period from the level of the carina to the diaphragm. Tomographic slices were ECG-gated and obtained at 60% to 80% of the R-wave to R-wave interval. Scans were considered of acceptable research quality only if the images were free from motion and from respiratory or arrhythmic artifacts. Coronary and cardiac valve calcification was quantified using the volume score as described previously (12). All of the scans were analyzed independently by two experienced investigators (P.R. and A.B.).

Study Outcome

The primary outcome was all-cause mortality. Mortality was verified by searching the Social Security Death Index (http://ssdi.rootsweb.com/cgi-bin/ssdi.cgi) master file using patients' names and social security numbers. Searches were conducted for events occurring through July 2010.

Statistical Analyses

Characteristics of the study population were calculated overall and by the number of calcified valves detected by echocardiography. For continuous variables, means and SDs were calculated, and linear trend across the number of calcified valves was assessed via least squares. For categorical variables, proportions were calculated, and associations were assessed with chi-squared tests.

For mortality analyses, follow-up time was calculated as the number of days between a participant's study examination and date of death, or July 6, 2010 for those who remained alive. The median follow-up time was 5.6 years, and the maximum follow-up was 6.5 years. Cumulative mortality curves were calculated for echocardiographically detected mitral and aortic valve calcification, separately, using the Kaplan–Meier method. Differences in cumulative mortality were assessed using log-rank tests. Unadjusted mortality rates and hazard ratios, initially adjusted for age and age, race, and gender, were calculated by mitral valve calcification and aortic valve calcification and by number of calcified valves. Subsequent models included additional adjustment for diabetes mellitus, ASCVD, and pulse pressure. Also, mortality rates and hazard ratios for mortality were calculated by tertile of a combined calcification-volume score (the sum of coronary artery, mitral valve, and aortic valve scores) measured on EBCT to estimate total cardiovascular calcification burden. All of the analyses were conducted in SAS version 9.1 (SAS Institute, Cary, NC).

Results

Characteristics of patients according to the number of calcified valves are shown in Table 1. Patients with calcified valves were older and less likely to be African American. All other characteristics were similar between groups. EBCT and echocardiography showed an agreement of 74% and 64% for the detection of mitral and aortic valve calcification, respectively.

There were a total of 59 deaths over a median follow-up of 5.6 years (maximum follow-up, 6.5 years). Figures 1 and 2 show the Kaplan–Meier cumulative mortality curves for patients with and without calcification of the mitral valve and the aortic valve. Mortality for patients with valvular calcification was higher than for patients without calcification (log-rank test, $P = 0.01$ for each comparison).

The presence of valvular calcification at either site (mitral or aortic valve) was associated with higher mortality rates (Table 2). However, after adjustment for age, gender,

Table 1. Characteristics of the study population by number of calcified valves (mitral and aortic)

	Overall Population (n = 144)	Number of Calcified Valves			P trend
		0 (n = 61)	1 (n = 47)	2 (n = 36)	
Age, years	55.4 (14.6)	52.0 (14.9)	56.5 (13.8)	59.7 (14.3)	0.03
Women, %	50.7	54.1	55.3	38.9	0.19
African American, %	53.5	62.3	48.9	44.4	0.07
Median time on dialysis, years (IQR)	2.6 (1.4, 5.7)	2.6 (1.3, 5.7)	2.2 (1.2, 5.5)	3.0 (2.1, 6.1)	0.50
History of ASCVD, %	38.9	34.4	44.7	38.9	0.56
Diabetes mellitus, %	50.0	49.2	44.7	58.3	0.47
Current smoker, %	18.1	17.2	25.0	11.1	0.58
Hypertension, %	95.1	96.7	95.7	91.7	0.29
Dyslipidemia, %	49.3	42.6	55.3	52.8	0.27
Pulse pressure, mmHg	67.5 (21.0)	64.8 (20.9)	67.2 (21.9)	72.3 (19.6)	0.23

The values in table are either the means (standard deviations) or percentages except time on dialysis and immunoreactive parathyroid hormone, which are median (25^{th}, 75^{th} percentiles). ASCVD, atherosclerotic cardiovascular disease; IQR, interquartile range.

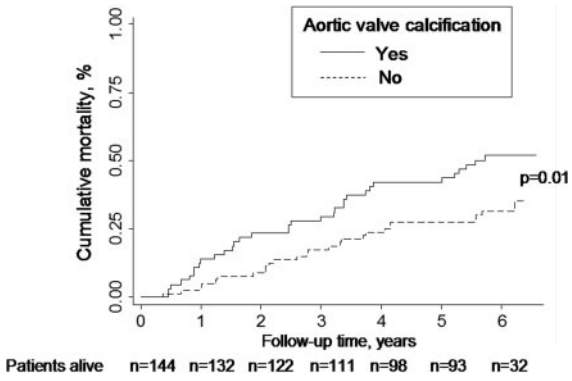

Figure 1. | Kaplan–Meier graph of all-cause mortality risk for patients with and without aortic valve calcification.

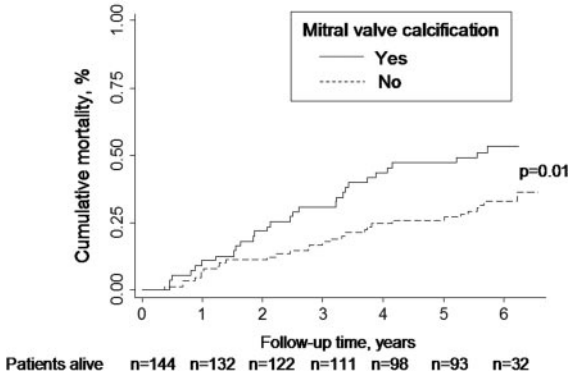

Figure 2. | Kaplan–Meier graph of all-cause mortality risk for patients with or without mitral-valve calcification.

race, diabetes mellitus, ASCVD, and pulse pressure, only mitral valve calcification remained associated with all-cause mortality (hazard ratio [HR] for presence *versus* absence of mitral valve calcification, 1.73; 95% confidence interval [CI], 1.03 to 2.91).

There was a graded increase in the risk for all-cause mortality associated with having one or two calcified cardiac valves (Table 3). Patients with two calcified valves had a two-fold increased HR for all-cause mortality during follow-up compared with patients without valvular calcification (HR, 2.16; 95% CI, 1.14 to 4.08). This association remained present after adjustment for age, gender, race, diabetes mellitus status, ASCVD, and pulse pressure (HR, 2.12; 95% CI, 1.12 to 4.01).

We further examined the association between a combined (continuous) score of coronary and valvular calcification measured on chest CT and all-cause mortality. As shown in Table 4, the combined score was associated with all-cause mortality during follow-up independent of age, race, gender, diabetes mellitus, and ASCVD (HR for the comparison of highest *versus* lowest tertile of the combined score, 2.21; 95% CI, 1.08 to 4.54).

Discussion

In this prospective observational study, we showed that valvular calcification, assessed qualitatively on transthoracic echocardiography, was associated with all-cause mortality over 5 years of follow-up, independent of several risk factors. Furthermore, a quantitative valvular and coronary calcification score measured on chest CT imaging was also associated with all-cause mortality during follow-up. These data expand the currently limited literature on the prognostic importance of valvular calcification in hemodialysis patients. Indeed, a single publication on hemodialysis patients preceded this study but showed a lack of association of valvular calcification with outcome once the model was adjusted for confounding variables (9). In another publication, mitral valve annulus calcification was associated with death from all causes, but the population was a combination of CKD-4 and CKD-5D patients including both peritoneal and hemodialysis (13). Furthermore, the authors presented results showing the association after multivariable adjustment. Finally, Wang *et al.* (8) found an association between valvular calcification and cardiovascular, as well as all-cause mortality in peritoneal dialysis patients.

Table 2. Mortality rates and hazard ratios for mortality associated with mitral valve calcification and with aortic valve calcification (*n* = 144)

	Mitral Valve Calcification			Aortic Valve Calcification		
	No (*n* = 89)	Yes (*n* = 55)	*P*	No (*n* = 80)	Yes (*n* = 64)	*P*
Deaths, *n*	30	29	—	26	33	—
Mortality rate, per 1000 person-years	67.9	128.7	0.01	65.3	122.7	0.01
Hazard ratio (95% confidence interval)						
adjusted for age	1	1.70 (1.01 to 2.85)	0.04	1	1.59 (0.93 to 2.70)	0.09
adjusted for age, race, and gender	1	1.64 (0.98 to 2.76)	0.06	1	1.50 (0.88 to 2.55)	0.14
adjusted for multiple factors[a]	1	1.73 (1.03 to 2.91)	0.04	1	1.52 (0.89 to 2.59)	0.12

[a]Adjusted for age, race, gender, diabetes mellitus status, history of atherosclerotic coronary vascular disease, and pulse pressure.

Table 3. Mortality rates and hazard ratios for mortality associated with calcified mitral and/or aortic valves (*n* = 144)

	Number of Calcified Valves			*P*
	0 (*n* = 61)	1 (*n* = 47)	2 (*n* = 36)	
Deaths, *n*	19	18	22	—
Mortality rate, per 1000 person-years	61.5	81.0	161.8	0.02
Hazard ratios (95% confidence interval)				
adjusted for age	1	1.18 (0.62 to 2.27)	2.16 (1.14 to 4.08)[b]	0.02
adjusted for age, race, and gender	1	1.11 (0.57 to 2.16)	2.00 (1.06 to 3.77)[b]	0.035
adjusted for multiple factors[a]	1	1.06 (0.54 to 2.08)	2.12 (1.12 to 4.01)[b]	0.02

[a]Adjusted for age, race, gender, diabetes mellitus status, history of atherosclerotic coronary vascular disease, and pulse pressure.
[b]$P < 0.05$ compared with those with no calcified valves.

Table 4. Mortality rates and hazard ratios for mortality associated with the combined calcification score

	Combined Calcification Score			*P*
	<93.1 (*n* = 48)	93.1 to 816.9 (*n* = 48)	>816.9 (*n* = 48)	
Deaths, *n*	12	18	29	—
Mortality rate, per 1000 person-years	47.8	80.8	150.1	<0.01
Hazard ratios (95% confidence interval)				
adjusted for age	1	1.57 (0.75 to 3.27)	2.57 (1.28 to 5.15)[b]	0.06
adjusted for age, race, and gender	1	1.41 (0.67 to 2.97)	2.31 (1.14 to 4.67)[c]	0.01
adjusted for multiple factors[a]	1	1.27 (0.59 to 2.72)[c]	2.21 (1.08 to 4.54)[c]	0.02

The score is a combination of the following plaque volumes: coronary arteries, mitral valve, and aortic valve (*n* = 144).
[a]Adjusted for age, race, gender, diabetes mellitus status, history of atherosclerotic coronary vascular disease, and pulse pressure.
[b]$P < 0.01$ compared with those with no calcified valves.
[c]$P < 0.05$ compared with those with no calcified valves.

Echocardiography is the gold standard for assessment of cardiac valve morphology and function; it is noninvasive and relatively inexpensive. Calcification of the cardiac valves is found in dialysis patients with a prevalence four to five times higher than in the general population (14–16). Ribeiro *et al.* (14) reported prevalence of mitral and aortic calcification of 44.5% and 52% in CKD-5D patients compared with 10% and 4.3%, respectively, in subjects with normal renal function ($P = 0.02$ and $P = 0.01$). In the same study, mitral and aortic calcification were significantly associated with peripheral arterial calcification ($P = 0.009$) and alterations of mineral metabolism (14). A similar prevalence of valvular calcification in hemodialysis was reported in several later randomized trials (17–19).

Although less frequent than vascular calcification, valvular calcification shares common risk factors and pathogenetic features (2,20). Although lipid and inflammatory cell infiltration of the aortic valve has been described in the general population with atherosclerotic disease (21), alterations of mineral metabolism have been involved in the development of valvular calcification in chronic kidney disease patients. The cell responsible for calcification of the

cardiac valves may be a myofibroblast, whereas a smooth muscle cell or a pericyte may be the cell initiating and sustaining vascular calcification. Of interest, in the Treat to Goal study (22), as well as the more recent ADVANCE study (19), valvular calcification progression was slowed by interventions that altered the metabolism of calcium, phosphorus, and parathyroid hormone in patients undergoing hemodialysis.

In the publication by Wang *et al.* (8) involving peritoneal-dialysis patients, all-cause and cardiovascular mortality did not differ significantly between patients with valvular calcification and those with a history of atherosclerotic vascular disease, reinforcing the hypothesis that valvular calcification represents a marker of systemic cardiovascular disease. In another publication, the same group showed an interaction between serum fetuin-A levels, malnutrition, inflammation, atherosclerosis, and valvular calcification in influencing adverse outcomes in 238 peritoneal dialysis patients (23). Valvular calcification has also been associated with other markers of atherosclerosis such as carotid intima-media thickness (24).

This study corroborates the notion that valvular calcification is a marker of systemic cardiovascular disease and a marker of increased mortality risk in CKD-5D patients. Valvular calcification progression was attenuated with the use of statins in the general population (25) and with sevelamer and cinacalcet treatment in CKD-5D patients (19,22). Whether slowing of progression will result in an overall risk reduction in these patients remains to be demonstrated.

This study should be interpreted in the context of a few potential limitations. The study was limited to hemodialysis patients seen at two high-volume centers, and the results should be confirmed in other cohorts. Echocardiograms were performed at a single time point, and some patients may have developed valvular calcification during follow-up. However, such misclassification most likely means that the true association between valvular calcification and mortality is stronger than we reported. We did not have information on the specific cause of death. As such, we were unable to assess the association of valvular calcification with cardiovascular mortality. The sample size for this study was relatively small. Although several of the hazard ratios we reported were large, the confidence intervals around these estimates were wide. With a more precise estimate, aortic valve calcification may indeed reveal a statistical association with mortality. Future studies attempting to address the relationship between valvular calcification and all-cause mortality should recruit larger sample sizes. The strengths of this study include the dual assessment (qualitative by echocardiography and quantitative by CT) of valvular calcification, the long follow-up of patients, and the careful adjustment of our prediction models for relevant variables.

In summary, the presence and extent of valvular calcification are associated with an increased risk of all-cause mortality in maintenance hemodialysis patients. These findings further support the use of a simple and noninvasive, nonradiologic test such as echocardiography for risk stratification of dialysis patients, as recently suggested in the international guidelines on mineral metabolism issued by the Kidney Disease Improving Global Outcomes panel of experts (26).

Disclosures

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References

1. Raggi P, Boulay A, Chasan-Taber S, Amin N, Dillon M, Burke SK, Chertow GM: Cardiac calcification in adult hemodialysis patients: A link between end-stage renal disease and cardiovascular disease? *J Am Coll Cardiol* 39: 695–701, 2002
2. Moe SM, O'Neill KD, Duan D, Ahmed S, Chen NX, Leapman SB, Fineberg N, Kopecky K: Medial artery calcification in ESRD patients is associated with deposition of bone matrix proteins. *Kidney Int* 61: 638–647, 2002
3. Fox CS, Vasan RS, Parise H, Levy D, O'Donnell CJ, D'Agostino RB, Benjamin EJ: Mitral annular calcification predicts cardiovascular morbidity and mortality: The Framingham Heart Study. *Circulation* 107: 1492–1496, 2003
4. Volzke H, Haring R, Lorbeer R, Wallaschofski H, Reffelmann T, Empen K, Rettig R, John U, Felix SB, Dorr M: Heart valve sclerosis predicts all-cause and cardiovascular mortality. *Atherosclerosis* 209: 606–610, 2010
5. Zhang Y, Safar ME, Iaria P, Lieber A, Peroz J, Protogerou AD, Rajzbaum G, Blacher J: Cardiac and arterial calcifications and all-cause mortality in the elderly: The PROTEGER Study. *Atherosclerosis* 213: 622–626, 2010
6. Barasch E, Gottdiener JS, Marino Larsen EK, Chaves PH, Newman AB: Cardiovascular morbidity and mortality in community-dwelling elderly individuals with calcification of the fibrous skeleton of the base of the heart and aortosclerosis (The Cardiovascular Health Study). *Am J Cardiol* 97: 1281–1286, 2006
7. Otto CM, Lind BK, Kitzman DW, Gersh BJ, Siscovick DS: Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. *N Engl J Med* 341: 142–147, 1999
8. Wang AY, Wang M, Woo J, Lam CW, Li PK, Lui SF, Sanderson JE: Cardiac valve calcification as an important predictor for all-cause mortality and cardiovascular mortality in long-term peritoneal dialysis patients: A prospective study. *J Am Soc Nephrol* 14: 159–168, 2003
9. Panuccio V, Tripepi R, Tripepi G, Mallamaci F, Benedetto FA, Cataliotti A, Bellanuova I, Giacone G, Malatino LS, Zoccali C: Heart valve calcifications, survival, and cardiovascular risk in hemodialysis patients. *Am J Kidney Dis* 43: 479–484, 2004
10. Bellasi A, Ferramosca E, Muntner P, Ratti C, Wildman RP, Block GA, Raggi P: Correlation of simple imaging tests and coronary artery calcium measured by computed tomography in hemodialysis patients. *Kidney Int* 70: 1623–1628, 2006
11. Achenbach S, Ropers D, Mohlenkamp S, Schmermund A, Muschiol G, Groth J, Kusus M, Regenfus M, Daniel WG, Erbel R, Moshage W: Variability of repeated coronary artery calcium measurements by electron beam tomography. *Am J Cardiol* 87: 210–213, 2001
12. Callister TQ, Cooil B, Raya SP, Lippolis NJ, Russo DJ, Raggi P: Coronary artery disease: Iymproved reproducibility of calcium scoring with an electron-beam CT volumetric method. *Radiology* 208: 807–814, 1998
13. Sharma R, Pellerin D, Gaze DC, Mehta RL, Gregson H, Streather CP, Collinson PO, Brecker SJ: Mitral annular calcification predicts mortality and coronary artery disease in end stage renal disease. *Atherosclerosis* 191: 348–354, 2007
14. Ribeiro S, Ramos A, Brandao A, Rebelo JR, Guerra A, Resina C, Vila-Lobos A, Carvalho F, Remedio F, Ribeiro F: Cardiac valve calcification in haemodialysis patients: Role of calcium-phosphate metabolism. *Nephrol Dial Transplant* 13: 2037–2040, 1998
15. Mazzaferro S, Coen G, Bandini S, Borgatti PP, Ciaccheri M,

Diacinti D, Ferranti E, Lusenti T, Mancini G, Monducci I, et al.: Role of ageing, chronic renal failure and dialysis in the calcification of mitral annulus. *Nephrol Dial Transplant* 8: 335–340, 1993
16. Straumann E, Meyer B, Misteli M, Blumberg A, Jenzer HR: Aortic and mitral valve disease in patients with end stage renal failure on long-term haemodialysis. *Br Heart J* 67: 236–239, 1992
17. Chertow GM, Burke SK, Raggi P: Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int* 62: 245–252, 2002
18. Block GA, Spiegel DM, Ehrlich J, Mehta R, Lindbergh J, Dreisbach A, Raggi P: Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. *Kidney Int* 68: 1815–1824, 2005
19. Raggi P, Chertow GM, Torres PU, Csiky B, Naso A, Nossuli K, Moustafa M, Goodman WG, Lopez N, Downey G, Dehmel B, Floege, J: The ADVANCE study: A randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. *Nephrol Dial Transplant* 2010
20. Raggi P, Giachelli C, Bellasi A: Interaction of vascular and bone disease in patients with normal renal function and patients undergoing dialysis. *Nat Clin Pract Cardiovasc Med* 4: 26–33, 2007
21. Mohler ER, 3rd: Mechanisms of aortic valve calcification. *Am J Cardiol* 94: 1396–1402, 2004
22. Raggi P, Bommer J, Chertow GM: Valvular calcification in hemodialysis patients randomized to calcium-based phosphorus binders or sevelamer. *J Heart Valve Dis* 13: 134–141, 2004
23. Wang AY, Woo J, Lam CW, Wang M, Chan IH, Gao P, Lui SF, Li PK, Sanderson JE: Associations of serum fetuin-A with malnutrition, inflammation, atherosclerosis and valvular calcification syndrome and outcome in peritoneal dialysis patients. *Nephrol Dial Transplant* 20: 1676–1685, 2005
24. Wang AY, Ho SS, Wang M, Liu EK, Ho S, Li PK, Lui SF, Sanderson JE: Cardiac valvular calcification as a marker of atherosclerosis and arterial calcification in end-stage renal disease. *Arch Intern Med* 165: 327–332, 2005
25. Pohle K, Maffert R, Ropers D, Moshage W, Stilianakis N, Daniel WG, Achenbach S: Progression of aortic valve calcification: association with coronary atherosclerosis and cardiovascular risk factors. *Circulation* 104: 1927–1932, 2001
26. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int* [suppl[: S1–S130, 2009

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