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Associations Between Coronary Calcification on Chest Radiographs and Mortality in Hemodialysis Patients

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Abstract

Background—KDIGO (Kidney Disease: Improving Global Outcomes) guidelines recommend lateral abdominal radiographs to assess vascular calcification in incident dialysis patients. However, nearly all dialysis patients in the US receive chest radiographs at dialysis inception which may provide readily available information on coronary artery calcification (CAC) and aortic arch calcification (AAC). We determined the prevalence of CAC and AAC visible on plain chest radiographs and their associations with mortality in our dialysis population.

Study Design—Retrospective Analysis

Setting & Participants—93 participants who received maintenance hemodialysis at the San Diego VAMC in 2009–2010

Predictor—Presence of CAC and AAC as evaluated by a radiologist

Outcome—All cause mortality

Results—The average age was 64; 22% were African-American, and 97% were male. CAC and AAC prevalence were 25% and 58%, respectively. During 20 months' follow-up, 28% died. CAC was strongly associated with mortality in models including cardiovascular (HR, 2.41; 95% CI 1.04–5.59) and dialysis-related (HR, 2.86; 95% CI 1.24–6.6) risk factors. AAC was associated with a HR of 5.25 (95% CI, 1.46–17.72) in cardiovascular risk-factor adjusted models and 7.31 (95% CI, 2.03–26.34) in dialysis models. When CAC and AAC were both included in models, both CAC (HR, 3.40; 95% CI, 1.24–9.36) and AAC (HR, 6.23; 95% CI, 1.64–23.66) remained significantly associated with mortality.

Limitations—The study sample is relatively small and mostly male.

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Conclusions—CAC and AAC are highly prevalent on chest radiographs in dialysis patients, and strongly associated with mortality independent of one another. Since these images are nearly ubiquitous, inexpensive, and often already obtained for other indications, they should be considered for risk assessment in hemodialysis patients. Future studies are required to determine whether CAC or AAC on chest radiography is additive or duplicative of the risk of aorto-iliac calcification on lateral abdominal radiographs currently suggested by KDIGO.

The estimated risk for mortality from cardiovascular events among patients treated by dialysis is over 10 times the risk of age-matched individuals in the general population,¹ and models developed for cardiovascular disease (CVD) risk prediction in the general population may not be as accurate in hemodialysis patients.² Possible contributing factors include alterations in calcium/phosphate homeostasis, abnormal lipid metabolism, prevalence of hypertension and diabetes, and chronic inflammation.^{3,4,5,6} Noninvasive radiographic imaging is gaining recognition as a simple and valid method of improving estimations of cardiovascular risk based on the extent and grade of detectable coronary artery calcification (CAC) in the general population^{7,8} and in selected dialysis populations as well.^{9,10} The importance of vascular calcification as a prognostic tool has already been recognized by the KDIGO (Kidney Disease: Improving Global Outcomes) group, which in a position statement in 2006 recommended screening via lateral abdominal radiographs for the presence of vascular calcifications in all incident dialysis patients.

In the general population, multidetector row computed tomography (CT) scans have become the predominant modality for estimating CAC¹¹ because calcification on these scans adds prognostic information that is independent of that included in the Framingham risk score for cardiac events and all-cause mortality.¹² In recent years, much less attention has been paid to the use of conventional chest radiographs as an imaging modality for evaluating coronary calcifications. Although generally known to be much less sensitive than CT scans for CAC detection in the general population,¹³ when utilized in a patient population with a high pretest probability for CAC such as the hemodialysis population, conventional chest radiographs – obtained in virtually all US patients at initiation of dialysis -- may serve as a valuable and readily available source of prognostic information regarding future cardiovascular events than previously recognized. Furthermore, if the presence of detectable calcifications on conventional chest radiographs provides important information, the much higher radiation exposure required for CT scans could be avoided in this population, which already undergoes many diagnostic radiology tests.¹⁴

We hypothesized that evaluation of conventional chest radiographs for CAC among hemodialysis patients would demonstrate an association with all-cause mortality. We further postulated that CAC would serve as a prognostic indicator in its own right after adjustment for aortic arch calcification (AAC) on chest radiographs, which has previously been shown to be a risk factor for mortality in dialysis patients.¹⁵

Methods

Participants

We identified all patients who underwent maintenance hemodialysis at the VA San Diego Healthcare System between May 2009 and September 2010 (N = 99). Patients were included if they had a frontal and lateral chest radiograph at the VA Medical Center, and if they had routine surveillance blood laboratory measurements performed during the study period.

Exclusion criteria included chest radiographs in which the presence of stents precluded accurate evaluation for CAC (n=4), and absence of a prior frontal and lateral chest radiograph (n = 2).

The study protocol was reviewed and approved by the University of California San Diego Institutional Review Board and the VA Research Service. Requirement for patient consent was waived due to the use of retrospective data and minimal participant risk.

Measurements

A radiologist specializing in thoracic radiology and blinded to patient information independently reviewed one pre-selected frontal and lateral chest radiograph obtained from each hemodialysis patient within or as close to the prespecified study period as possible. Chest frontal and lateral views were obtained with 140 kVp on a direct digital radiography chest unit (Philips Digital Diagnost). The lateral view was inspected for potential coronary calcifications in characteristic locations pertaining to the course of the coronary arteries. In the frontal projection, the previously designated CAC triangle¹³ was surveyed for visible CAC. The CAC triangle refers to a triangular region of the frontal chest film demonstrated to be valuable for visualization of CAC. It is the region outlined by the vertebral column as the medial border, the upper half of the left lateral cardiac margin as the hypotenuse, and a horizontal line as the inferior border (figure 1a). CAC is readily distinguishable from epicardial calcifications, as the latter tend to conform to the external cardiac contour, are thin and curvilinear, and don't conform to the anatomical course of the coronary arteries in either the frontal or the lateral projection. The aortic arch was inspected for the presence of calcifications on the frontal view for AAC.

Intra-reader reliability was assessed by repeat evaluation by the same radiologist of 20 chest radiographs randomly selected from the original data set. This review occurred 6 weeks after the initial reading. Agreement was assessed using kappa (k) statistics, which estimates the agreement beyond what is expected due to chance alone. A value of zero for k suggests the result is as expected due to chance, and a value of 1 suggests perfect agreement.

Covariates

Serum creatinine was measured using the enzymatic method by a Roche Diagnostics Cobas 6000 machine. Coefficients of variation were <2%. Blood specimens were obtained previously as part of routine monthly laboratory assessments, and were delivered directly to the clinical laboratory on site at the same facility as our dialysis unit. Serum albumin, urea nitrogen, lipids, calcium, and phosphorus were measured predialysis on the mid-week dialysis session (Wednesday or Thursday) by using routine laboratory methods. Intact PTH was measured using the Elecsys assay, a two step sandwich immunoassay (reference range, 15–75 pg/ml). Age, sex, race; history of diabetes (DM), stroke, peripheral arterial disease (PAD), angioplasty, stenting, coronary artery bypass graft (CABG) surgery, and smoking were obtained through chart review. Coronary artery disease (CAD) was defined as previous history of CABG, angioplasty, or stenting as determined through chart review. Hyperlipidemia was defined as total cholesterol greater than 200mg/dl or use of any lipid lowering medication. Dialysis vintage was determined from date of maintenance hemodialysis initiation recorded in the VA dialysis unit records. Systolic and diastolic blood pressures were measured with an automated sphygmomanometer prior to maintenance dialysis. Predialysis weights were measured by scale at each dialysis session. Height was obtained from the most recent value recorded in the medical record. BMI was calculated by postdialysis mass in kilograms divided by the square of height in meters.

Outcome

Patient deaths during the study period were determined from review of the VA-computerized medical record, which includes deaths that occur at outside hospitals or at home, in addition to dates and circumstances of death. We had 100% ascertainment for death among the 93 study participants.

Statistical methods

Participant characteristics were compared between groups with or without CAC visible on chest radiographs. Descriptive statistics were calculated using mean $\pm$ SD or median (25th–75th percentile) for skewed variables. P values for Chi square, t test, or Mann-Whitney U test (for skewed variables) were computed, as appropriate. We considered covariates for inclusion in our multivariate models based on differences between the two groups with $p < 0.10$ or biological plausibility. We limited the number of covariates in final models to no more than 6 to avoid model overspecification.

We examined Kaplan-Meier plots of survival with Hall-Wellner bands¹⁶ based on CAC or AAC categories. Cox proportional hazard regression models were constructed to evaluate the independent hazard associated with CAC or AAC. The assumption of proportional hazards was verified by examination of negative log-log survival curves. Because of the limited number of outcomes in this data set, we proceeded with limited covariate adjustments as follows: Our first model included CAC adjusted for demographic variables (age and race). Our second model was adjusted for the risk factors traditionally associated with cardiovascular morbidity including age, CAD, diabetes, hyperlipidemia, and hypertension. Our third model was adjusted for dialysis specific factors associated with mortality, including age, serum phosphorus, albumin, dry weight, dialysis vintage, and predialysis creatinine. We then considered mutual adjustment of CAC for AAC in a joint model, also adjusting for factors independently associated with mortality based on univariate analysis. This included age, CAD, diabetes, phosphorus, hyperlipidemia, and predialysis creatinine.

All analyses were conducted using SAS statistical software version 9.3.

Results

Overall, 24.7% ($n = 23$) of the cohort had visible CAC on chest film, and 58% ($n = 54$) had AAC; during a median of 1.8 years of follow-up, 26 deaths occurred in the study population. Representative examples of CAC and AAC on chest radiographs are shown in figures 1b–1d. The average age of the maintenance hemodialysis patients with CAC was 66 ± 11 years, versus 63.3 ± 10 without CAC ($p < 0.01$) (table 1). Only three patients were female, reflecting the gender distribution of our VA hemodialysis population. Coronary artery disease was present in 70% of the patients with CAC, and 39% of the patients without CAC ($p < 0.01$). PAD was present in 48% of the patients with CAC, as compared to 20% of the patients without CAC ($p < 0.01$). There was no significant difference between CAC groups in prevalence of hyperlipidemia, smoking history, diabetes, serum albumin, dialysis vintage or predialysis creatinine.

Participants with CAC or AAC were at greater risk of death in unadjusted analysis (Figures 2 and 3; $p < 0.001$ for each).

In Cox regression, CAC presence conferred a nearly three-fold risk of death in a model adjusted for age and ethnicity (model 1), as demonstrated in table 2. With adjustment for traditional cardiovascular risk factors (model 2), the risk was greater than two-fold. In a third model adjusting for dialysis-related factors (age, phosphorus, predialysis creatinine, albumin, BMI, dialysis vintage), CAC was also associated with an approximately 3-fold higher death risk. Lastly, in a final model (model 4; table 2) that included covariates that were associated with mortality in univariate analysis (table 3), the association of CAC with death was slightly stronger, and remained highly statistically significant.

We evaluated AAC prevalence with mortality through the same sequence of models. Based on the point estimates, AAC was consistently more strongly associated with death than CAC, with hazard ratios ranging from 5 to 7 fold higher risk compared to those without AAC (Table 3).

When CAC and AAC were entered into models jointly, both variables remained strongly associated with death independent of one another, albeit the point estimates were consistently modestly attenuated compared to models that included CAC or AAC separately (Table 3).

Among the 20 radiographs selected for repeat evaluation for CAC, 16 (80%) received a consistent evaluation ($k = 0.54$), indicating moderate agreement¹⁷. Upon repeat evaluation for AAC, 20/20 received a consistent evaluation ($k = 1$), indicating perfect agreement.

Discussion

In our single-center cohort, we found a high prevalence of CAC visible on chest radiographs. This finding was associated with a two- to three-fold greater risk of all-cause mortality which was not attenuated by adjustment for standard cardiovascular, dialysis related risk factors, or the presence of AAC. AAC was also highly prevalent on chest radiograph, and even more strongly associated with death. To our knowledge, this is the first study to demonstrate that CAC observed on conventional chest radiography is independently associated with mortality in hemodialysis patients.

It has previously been noted that CAC is much more common among ESRD patients than their age and sex matched counterparts in the general population.¹⁸ Previous studies have suggested that the prevalence of CAC among hemodialysis patients^{19,20} is well above 50%. Goodman and colleagues⁹ demonstrated that 14 of 16 hemodialysis patients between 20 and 30 years of age had coronary calcification detectable by electron beam CT scans. Furthermore, CAC scores increase in less than two years in many hemodialysis patients.²¹ Although calcifications in these studies were evaluated using CT scans, this information provides a conceptual framework for understanding the highly prevalent and progressive nature of CAC among hemodialysis patients. It also highlights the utility of assessment for the disease. Our study has shown that a simple, qualitative assessment of chest radiographs for coronary arterial calcifications is associated with substantially increased rates of mortality, even after adjustment for common confounders. Our cohort had a CAC prevalence of 25%, well below what has been described in studies using CT scans in dialysis patients, despite the fact that our cohort is comprised predominantly of older men. This suggests, as we expected, that chest radiographs are less sensitive for CAC detection; however, the high mortality rate among those with CAC in our study suggests that CAC visible on chest radiography may be more severe, and that this technique may be more sensitive in detecting clinically significant disease in this patient population.

Our findings are consistent with prior studies evaluating the association between various anatomic regions of arterial calcifications and mortality in hemodialysis patients, including abdominal aortic²² and peripheral vascular calcifications²³ as assessed by conventional radiography of the abdomen and extremities. The advantage of utilizing conventional chest radiographs is that in many cases hemodialysis patients have already had at least one (if not multiple) such studies for other indications, frequently simply as a requirement for entry into a dialysis unit²⁴. Thus, chest radiographs obtained in the course of usual clinical practice may be a good substitute, instead of a separately ordered lateral abdominal radiograph, to fulfill the NKF-KDOQI (National Kidney Foundation's Kidney Disease Outcomes Quality Initiative) vascular screening recommendation.^{24a}

Electron beam CT scans have previously been studied in hemodialysis patients, and multidetector row CT scans are being increasingly utilized for cardiovascular risk assessment. However, the appropriate clinical indication for their use in hemodialysis patients remains debatable. The ACCF/AHA consensus statement²⁵ on CAC scoring among ESRD patients deemed the indications for CT scanning “unclear” due to limited available clinical studies and outcomes data. This ambiguity further strengthens the argument that conventional chest radiography may serve as a reasonable alternative until the role of CT scanning is better defined. Financial implications also deserve consideration, as the cost of a chest radiograph is approximately 10%–15% of the cost of a CT scan.²⁶ Furthermore, CT scans may not be as easily accessible in certain regions or healthcare systems as in the United States.²⁷

CT scans utilized in CAC scoring vary in the radiation dose, with estimations of 1 – 6.2 mSv depending on type of CT scan and scanning protocol used. A frontal and lateral chest radiograph exposes the average patient to 0.06 mSv of radiation,²⁸ thus approximately 2 orders of magnitude less than chest CT. In addition, the cumulative radiation dose that maintenance hemodialysis patients receive, likely related to multiple chronic illnesses, is substantial and greater than that of the general population^{14,29}. Radiation exposure may be particularly relevant in this patient population, who are potentially at higher risk for the development of malignancies³⁰.

As mentioned previously, given the suggestion of a link between disordered mineral and bone metabolism and increased risk for cardiovascular calcification³¹, the KDIGO released a position statement in 2006 recommending lateral abdominal radiographs as a screening tool for the presence of vascular calcifications in all incident dialysis patients.³² Given the ubiquity of chest radiographs among dialysis patients and the strong associations of both CAC and AAC with death observed here, chest radiographs may serve as a readily available and cost-effective alternative. On the other hand, lateral abdominal radiographs may be more sensitive for vascular calcification, as only approximately 25% of our patients had CAC on chest radiograph, and 58% had AAC, whereas the prevalence of vascular calcification on lateral abdominal radiograph was much higher (57–81%) in prior studies^{22,33} in hemodialysis patients. Future studies are needed to compare the prevalence of calcification in a single representative cohort, and to determine which anatomic location is most strongly associated with future mortality and CVD events. Of note, although it is speculated that hyperphosphatemia is related to CV calcifications¹⁵, lower phosphorus, rather than higher phosphorus, was associated with mortality in our cohort, which is likely related to its role as a surrogate marker for malnutrition.³⁴

We confirm findings of previous studies showing strong associations of aortic arch calcifications on chest radiographs with mortality.^{35,36,37} However, we extend these findings by demonstrating for the first time that AAC and CAC were each independently associated with mortality. If confirmed, this finding suggests that multiple radiographs (chest and abdomen, for example) may be helpful to measure the systemic burden of calcification, in order to optimize risk stratification in high-risk dialysis patients. Furthermore, given the independent prognostic information each provides, our findings suggest that if radiologists routinely reported the presence of both CAC and AAC on radiographs of hemodialysis patients, it may help the practicing nephrologist identify patients at particularly high risk of death.

Our study has important limitations. The study sample is relatively small. We examined patients at a VA dialysis center, thus most were men, making the generalizability to women uncertain. Our radiographs were reviewed by a radiologist specializing in thoracic radiology who was specifically examining the images for these calcifications; retrospective review of

dictated reports may not reveal these otherwise incidental findings. Concurrent data on chest CT scans or lateral abdominal radiographs are not available, and as such, direct comparison between the relative prevalence, sensitivity, specificity, and strengths of association with mortality by different imaging modalities is unknown. We were also unable to evaluate adjudicated causes of death among our cohort, so we were unable to determine whether cardiovascular mortality in particular was associated with the presence of cardiovascular calcifications.

In summary, chest radiographs, nearly universally available in dialysis patients, are inexpensive, involve low-radiation dose, and provide a method for assessing CAC and AAC in hemodialysis patients. Prevalent CAC and AAC are each associated with mortality, and both provide information about death risk independent of one another. This simple and ubiquitous imaging modality may hold promise for cardiovascular risk assessment in hemodialysis patients, and as such calcifications of the aortic arch and of the coronary arteries should be specifically mentioned by radiologists in their chest radiographic reports.

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Figure 1. Assessing CAC. (A) Anatomic Location of CAC triangle (shaded region). Outlined are the characteristic locations of the coronary arteries (1, Left Anterior Descending coronary artery; 2, Left Circumflex coronary artery; 3, Right coronary artery). Image courtesy of H.E. Starck. (B–C) Lateral chest radiographs showing heavy calcification of the Left Anterior Descending Coronary Artery (arrows). (D) Frontal chest radiograph demonstrating heavy calcification of the Aortic Arch (arrows).

Figure 2. Kaplan Meier curves for patients with and without CAC. Product-limit survival estimates are shown with 95% Hall-Wellner bands.

Figure 3. Kaplan Meier curves for patients with and without AAC. Product-limit survival estimates are shown with 95% Hall-Wellner bands.

Table 1

Demographic Characteristics of Participants

Clinical Variables	CAC Absent (n =70)	CAC Present (n = 23)	P	AAC Absent (n = 39)	AAC Present (n =54)	P
Age (y)	63.3 ± 10	66 ± 11	0.005	61.2 ± 8.9	67.9 ± 11	0.002
Male sex	68 (97%)	22 (96%)	0.7	36 (92%)	54 (100%)	0.04
African American	17 (24%)	3 (13%)	0.3	13 (33%)	7 (13%)	0.02
CAD	27 (39%)	16 (70%)	0.009	13 (33%)	30 (56%)	0.03
PAD	14 (20%)	11 (48%)	0.009	7 (18%)	18 (33%)	0.1
Dialysis Vintage (y)	2.9 (2.2–4.7)	2.9 (2.1–7.2)	0.5	2.5 (2.1–3.2)	3.7 (2.4–7)	0.1
Diabetes Mellitus	47 (67%)	17 (73%)	0.5	28 (72%)	36 (67%)	0.6
Calcium (mg/dl)	9.1 ± 0.6	9.0 ± 0.7	0.5	9.1 ± 0.7	9.0 ± 0.6	0.8
Phosphorus			0.4			0.8
<3.5 mg/dl	6 (9%)	3 (13%)		3 (8%)	6 (11%)	
3.5–5.5 mg/dl	33 (47%)	7 (30%)		16 (41%)	24 (44%)	
>5.5 mg/dl	31 (44%)	13 (57%)		20 (51%)	24 (44%)	
Hypertlipidemia	61 (87%)	21 (91%)	0.6	33 (85%)	49 (91%)	0.4
Albumin (g/dl)	3.7 ± 0.54	3.8 ± 0.62	0.4	3.6 ± 0.57	3.7 ± 0.57	0.8
Smoking History	51 (73%)	14 (61%)	0.3	26 (67%)	39 (72%)	0.6
BMI (kg/m ²)	26.6 ± 7.3	24.7 ± 4.6	0.2	27 ± 7.4	25.5 ± 6.2	0.3
Dry weight (kg)	83.8 ± 24	73.2 ± 13.29	0.05	86 ± 25.4	77.6 ± 19.2	0.07
SBP (mmHg)	143 ± 28	150 ± 31	0.4	149 ± 28	143 ± 29	0.3
DBP (mmHg)	78 ± 16	75 ± 17	0.5	84 ± 17	73 ± 15	0.002
Predialysis SCr (mg/dl)	7.0 ± 2.6	6.9 ± 3.0	0.9	7.1 ± 2.5	6.8 ± 2.9	0.7
AAC	34 (49%)	20 (87%)	0.001	--	--	--
CAC	--	--	--	3 (8%)	20 (37%)	0.001

Values for continuous variables are presented as mean ±/– standard deviation or median (25th–75th percentile); values for categorical variables are given as number (percentage). P values are for chi square or t-test as appropriate.

Abbreviations: AAC, aortic arch calcification; BMI, body mass index; CAC, coronary artery calcification; CAD, coronary artery disease; DBP, diastolic blood pressure; PAD, peripheral artery disease; SBP, systolic blood pressure; SCr, serum creatinine.

Table 2

Individually and mutually adjusted relationships of CAC and AAC on chest radiograph with mortality in hemodialysis patients

	CAC	AAC	CAC after adjustment for AAC	AAC after adjustment for CAC
Model 1: Demographic ¹	2.76(1.21–6.32)	6.89(1.95–24.35)	2.13(0.93–4.92)	6.19(1.71–4.92)
Model 2: Cardiac ²	2.41(1.04–5.59)	5.25(1.48–18.58)	1.84(0.78–4.35)	4.46(1.24–16.11)
Model 3: Dialysis Related ³	2.86(1.24–6.6)	7.31(2.03–26.34)	2.25(0.96–5.29)	6.59(1.78–24.42)
Model 4: Integrated ⁴	4.18(1.58–11.07)	7.13(1.94–26.16)	3.40(1.24–9.36)	6.23(1.64–23.66)

Values shown are Hazard Ratios (95% CI).

Abbreviations: AAC, aortic arch calcification; BMI, body mass index; CAC, coronary artery calcification; CAD, coronary artery disease

¹Model 1: CAC adjusted for age, ethnicity (African American) and subsequently AAC

²Model 2: CAC adjusted for age, CAD, diabetes, hyperlipidemia, hypertension, and subsequently AAC

³Model 3: CAC adjusted for age, phosphorus, predialysis creatinine, albumin, BMI, dialysis vintage and subsequently AAC

⁴Model 4: CAC adjusted for age, CAD, diabetes, predialysis creatinine, phosphorus, hyperlipidemia and subsequently AAC

Table 3

Univariate Association of Risk Factors with Mortality

Variable	Univariate HR for Mortality (95% CI)
Age (per 5 y older)	1.28 (1.08–1.52)
African American	0.89 (0.33–2.36)
History of Coronary Artery Disease	3.14 (1.36–7.24)
Dialysis Vintage (per 1-y greater)	0.97 (0.88–1.08)
Diabetes Mellitus	1.22 (0.51–2.90)
Phosphorus ^a	
<3.5mg/dl	4.05 (1.43–11.43)
> 5.5 mg/dl	0.997 (0.41–2.41)
Hyperlipidemia	1.55 (0.36–6.63)
Albumin (per 1-g/dl increase)	0.87 (0.43–1.76)
Smoking History (ever vs never)	0.58 (0.26–1.26)
BMI (per 1-kg/m ² increase)	0.94 (0.89–1.00)
Dry weight (per 1-kg increase)	0.98 (0.97–1.00)
History of hypertension	0.63 (0.29–1.36)
Predialysis SCr (per 1-mg/dl increase)	0.78 (0.66–0.93)
History of stroke	1.08 (0.45–2.57)
Presence of AAC	7.23 (2.17–24.10)
Presence of CAC	1.36 (1.07–1.72)

^a compared to a reference group of 3.5–5.5mg/dl

Abbreviations: AAC, aortic arch calcification; BMI, body mass index; CAC, coronary artery calcification; HR, hazard ratio; CI, confidence interval; SCr, serum creatinine