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Impact of abdominal aortic calcification on long-term cardiovascular outcomes in patients with chronic kidney disease

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ABSTRACT

Background: The presence of abdominal aortic calcification (AAC) can predict cardiovascular (CV) outcomes in hemodialysis patients. However, little is known about the predictive value of AAC for CV outcomes in chronic kidney disease (CKD) patients without hemodialysis. The aim of this study was to investigate the prevalence and the predictive value of AAC in asymptomatic CKD patients.
Methods: We prospectively evaluated 347 asymptomatic CKD patients without hemodialysis [median estimated glomerular filtration rate (eGFR): 43.2 mL/min/1.73 m^2]. A non-contrast computed tomography scan was used to determine the abdominal aortic calcification index (ACI) as a semi-quantitative measure of AAC. The patients were divided into three groups according to the tertiles of ACI.
Results: Among the subjects, AAC was found (ACI > 0) in 296 patients (86.3%), and the median ACI was 11.4%. During the median follow-up of 41.5 months, a total of 33 CV events were observed. Patients with the highest tertile of ACI had the highest risk of CV outcomes compared with the other two groups (96.5%, 93.0%, and 74.3%, respectively; $p < 0.001$). The Cox proportional hazard models showed that ACI was an independent predictor of CV outcomes (hazard ratio 1.36, 95% confidence interval 1.17–1.60, $p < 0.001$). The C-index was also significantly increased by adding eGFR and ACI values to the model along with the other conventional risk factors (0.79 versus 0.66, $p = 0.043$).
Conclusion: Evaluation of the AAC provides useful information for predicting adverse clinical outcomes among asymptomatic CKD patients without hemodialysis.
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1. Introduction

Chronic kidney disease (CKD) is closely related to increased morbidity and mortality of cardiovascular (CV) disease [1–4]. Moreover, patients with CKD frequently experience CV events associated with accelerated atherosclerosis and vascular calcification before the initiation of hemodialysis [5–7]. Thus, risk stratification for clinical events is clinically important in such populations. One of the main factors for the heightened CV risk in this population is the presence of mineral bone disorders (MBD), which is indicated by an imbalance of serum calcium, phosphorus, and parathyroid hormone (PTH) [8–11].

On the other hand, abdominal aortic calcification (AAC) detected by lumbar radiographs is also associated with increased risk of CV events [12,13]. Semi-quantitative methods, such as noncontrast computed tomography (CT) scans, for the assessment of AAC are highly sensitive for the earlier and precise detection of aortic calcification than previous qualitative methods, such as plain X-ray films. In the present study, we hypothesized that the AAC as detected by CT scans would be a useful indicator of future CV events, and could be used to identify high-risk patients with adverse CV outcomes in patients with CKD. Therefore, the aim of

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this study was to evaluate the predictive ability of the abdominal aortic calcification index (ACI) for future CV events in asymptomatic CKD patients without hemodialysis.

2. Materials and methods

2.1. Subjects

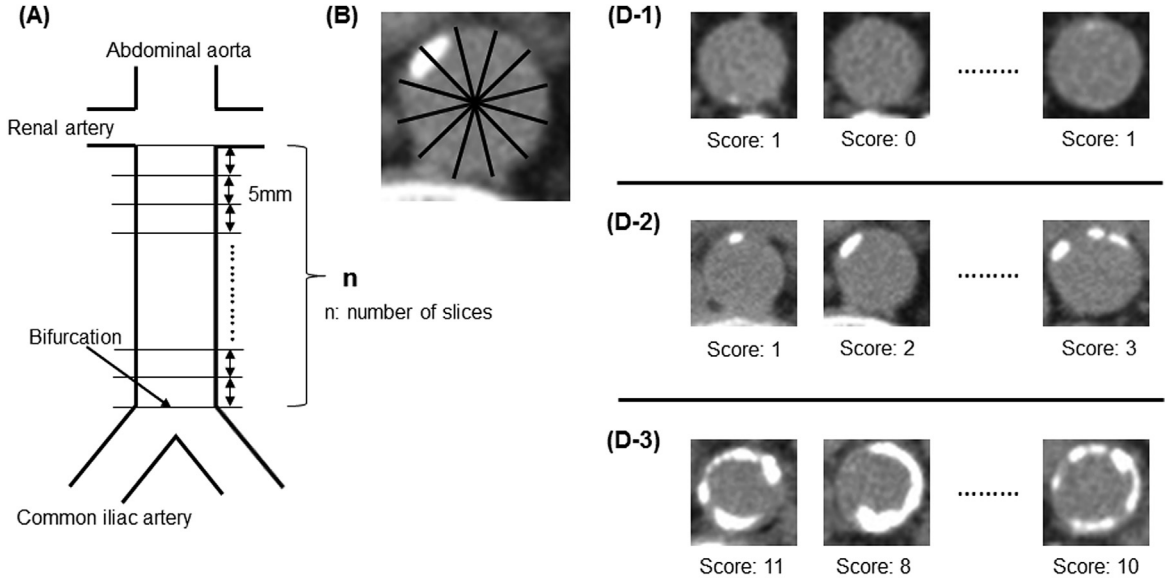
We prospectively evaluated 347 asymptomatic CKD patients without hemodialysis in the outpatient clinic at the Department of Nephrology in Nagoya University Hospital from November 2008 to October 2012. Patients with an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 or the presence of proteinuria and renal disease as a complication at study entry, or both, were defined as having CKD [14]. To investigate the renal morphology and degree of subclinical atherosclerosis in individuals, AAC were quantified by noncontrast CT scan, and the relationships between AAC and the clinical outcomes were analyzed. Clinical outcomes were defined as CV death, nonfatal stroke, nonfatal myocardial infarction, angina pectoris requiring revascularization, and heart failure requiring admission. Patient exclusion criteria were hemodialysis, active malignancy, and had undergone previous abdominal aortic artery repair or stenting. This study was approved by the local ethics committee, and was conducted in accordance with the ethical principles stated by the Declaration of Helsinki. Written informed consent was obtained from all patients. Body mass index (BMI) was calculated as body weight divided by height squared (kg/m^2). Hypertension was defined as systolic blood pressure (SBP) of ≥140 mmHg, diastolic blood pressure of ≥90 mmHg, and/or receiving hypertensive treatments. Diabetes mellitus (DM) was defined as the use of any anti-hyperglycemic medication, a current diagnosis of diabetes and/or having a fasting plasma glucose concentration of >126 mg/dL and/or a glycosylated hemoglobin concentration of ≥6.5% (National Glycohemoglobin Standardization Program). Dyslipidemia was defined as low-density lipoprotein cholesterol ≥140 mg/dL, high-density lipoprotein cholesterol ≤40 mg/dL, triglycerides ≥150 mg/dL, and/or receiving hyperlipidemia treatments. Current smokers were defined as those who declared active smoking at all available examinations.

2.2. Data collection

After an overnight fast of 12 h, blood samples were obtained from all patients. Serum creatinine was measured using the isotope-dilution mass spectrometry traceable enzymatic method, and the eGFR was calculated using the equation for Japanese subjects recommended by the Japanese Society of Nephrology: e-GFR (mL/min/1.73 m^2) = $194 \times SCr^{-1.094} \times age^{-0.287} \times 0.739$ (if female) [15]. The eGFR levels were classified according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guidelines (eGFR ≥ 90, 60–89, 45–59, 30–44, 15–29, and <15 mL/min/1.73 m^2 for G1, G2, G3a, G3b, G4, and G5, respectively) [14]. Serum calcium levels were corrected for albumin using the following formula: corrected calcium = total calcium + (4.0 − albumin) × 0.8, if albumin was <4.0 g/dL. Intact PTH was measured by electrochemiluminescence immunoassay (Roche Diagnostics, Tokyo, Japan).

2.3. Measurement of the abdominal aortic calcification index

All patients were scanned in the supine position in the craniocaudal direction using a 64-slice non-contrast CT scan (Siemens Medical Solutions, Forchheim, Germany), from which images were obtained with a 5-mm slice thickness. Calcification was considered



(C)

$$ACI\ (\%) = \frac{(\text{total score for calcification in all slices})}{12 \times n} \times 100$$

Fig. 1. The method of calculating aortic calcification index (ACI). (A) The images were obtained from the takeoff of the renal artery to the bifurcation of the aorta into the common iliac arteries at 5-mm intervals. (B) The cross-section of the abdominal aorta on each slice was divided into 12 radial segments. The number of calcified segments was counted on each slice. (C) This formula was used to calculate the ACI. (D) Representative cross-sectional images of the abdominal aorta in patients with 2.9% (D-1), 15.7% (D-2), and 50.8% ACI (D-3).

to be present if an area of ≥1 mm^2 displayed a density of ≥130 Hounsfield units. As shown in Fig. 1, the AAC score was calculated from the takeoff of the renal artery to the bifurcation of the aorta into the common iliac arteries. The cross-section of the abdominal aorta on each slice was radially divided into 12 segments. The ACI was calculated as follows: ACI = (total score for calcification on all slices)/12 × 1/(number of slices) × 100 (%) [16,17]. Semi-quantitative measurement of AAC was conducted independently by two physicians who were blinded to the patient's clinical characteristics. The inter- and intra-observer variability of ACI were well correlated [$r = 0.98$ ($p < 0.001$) and $r = 0.99$ ($p < 0.001$), respectively].

2.4. Statistical analysis

Data for normally distributed continuous variables were expressed as the mean ± standard deviation (SD). Continuous variables that were not normally distributed were expressed as the median (interquartile range). Categorical variables were expressed as numbers (percentages), while continuous variables were compared using one-way ANOVA (among the three groups with normal distribution), Student's *t*-test (among the two groups with normal distribution), or the Kruskal–Wallis test (among the three groups with non-normal distribution). Categorical variables were compared using the chi-square test or Fisher's exact test. Event-free survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. In the Kaplan–Meier method, only the day of the first outcome was considered as the day of the CV event in case of multiple outcomes in one patient. Interaction analyses were performed using Cox proportional hazards models. The ability of ACI to predict CV outcomes was examined by receiver operating characteristic (ROC) curve analyses. Moreover, the C-index was calculated to assess whether the accuracy of predicting CV outcomes would improve after adding eGFR levels and ACI into the baseline model along with the traditional CV risk factors. The statistical significance of the difference was estimated, as proposed by DeLong et al. [18]. A two-sided *p* value of <0.05 was considered statistically significant. SPSS version 18.0 for Windows (SPSS, Inc., Chicago, IL, USA) was used to perform all statistical analyses.

3. Results

A total of 347 patients were enrolled in the present study. The mean age was 67.4 ± 12.3 years, and the median eGFR level was 43.2 mL/min/1.73 m^2. Among the subjects, 34.9% of patients had DM, and 84.1% had hypertension. In the CT evaluations, the presence of AAC (defined as ACI > 0) was detected in 296 patients (85.3%), and the median ACI was 11.4%. Patients were divided into three groups according to the tertiles of ACI as follows: tertile 1, ACI <3.7%; tertile 2, 3.7% ≤ ACI <23.5%; and tertile 3, ACI ≥23.5%. Table 1 shows the baseline clinical characteristics of the study patients in the three groups. Moreover, Supplementary Table 1 shows the clinical characteristics among the CKD stages. As shown in Supplementary Figure, ACI increased with progression in CKD stage (1.3%, 5.6%, 8.1%, 12.0%, and 23.5% for G1, G2, G3a, G3b, and G4–5, respectively; *p* for trend < 0.001).

During the median follow-up of 41.5 months, a total of 33 CV

Table 1
Baseline characteristics among groups according to the tertiles of ACI.

Variables	ACI			*P* Value
	<3.7% (n = 115)	3.7%–23.5% (n = 116)	≥23.5% (n = 116)	
Demographics				
Male, n (%)	72 (62.6)	83 (71.6)	87 (75.0)	0.11
Age, years	59.2 ± 13.4	69.2 ± 9.7	73.7 ± 8.6	<0.001
Body mass index, kg/m^2	24.3 ± 5.0	23.7 ± 2.9	23.4 ± 3.0	0.36
Hypertension, n (%)	77 (67.0)	101 (87.1)	114 (98.3)	<0.001
Diabetes, n (%)	27 (23.5)	40 (34.5)	54 (46.6)	0.001
Dyslipidemia, n (%)	81 (70.4)	87 (75.0)	93 (80.2)	0.23
Current smoker, n (%)	12 (10.8)	9 (7.8)	17 (14.9)	0.23
Prior coronary artery disease, n (%)	1 (0.9)	5 (4.3)	22 (19.0)	<0.001
Prior stroke, n (%)	4 (3.5)	15 (12.9)	16 (13.8)	0.016
Systolic blood pressure (mmHg)	127.2 ± 15.4	131.1 ± 17.9	135.6 ± 19.2	0.002
Laboratory data				
Serum creatinine (mg/dL)	1.10 (0.79–1.53)	1.26 (0.91–1.62)	1.49 (1.13–1.96)	<0.001
eGFR (ml/min/1.73 m^2)	50.5 (36.9–66.1)	42.6 (30.4–57.2)	34.7 (25.3–49.6)	<0.001
Triglycerides (mg/dL)	132 (91–179)	139 (105–192)	128 (89–172)	0.17
LDL-C (mg/dL)	110 (93–129)	109 (90–124)	98 (78–120)	0.004
Hemoglobin A1c (%)	5.7 (5.4–6.2)	5.7 (5.4–6.2)	5.8 (5.5–6.5)	0.25
Hemoglobin (g/dL)	13.1 ± 2.0	12.9 ± 1.7	11.8 ± 1.8	<0.001
Serum albumin (g/dL)	3.9 ± 0.5	3.8 ± 0.4	3.7 ± 0.5	<0.001
Corrected calcium (mg/dL)	9.6 ± 0.4	9.5 ± 0.4	9.5 ± 0.4	0.48
Phosphorus (mg/dL)	3.4 ± 0.6	3.3 ± 0.6	3.5 ± 0.7	0.077
Intact PTH (pg/mL)	42.4 (32.4–59.5)	50.9 (39.1–71.7)	59.5 (41.4–89.6)	0.001
Medications				
Antiplatelet agent, n (%)	15 (13.0)	36 (31.0)	54 (46.6)	<0.001
ACE-I or ARB, n (%)	58 (50.4)	81 (69.8)	88 (75.9)	<0.001
Beta-blocker, n (%)	2 (1.7)	17 (14.7)	23 (19.8)	<0.001
Calcium channel blocker, n (%)	31 (30.4)	65 (56.0)	84 (72.4)	<0.001
Statin, n (%)	24 (20.9)	49 (42.2)	59 (50.9)	<0.001
Anti-diabetes drugs, n (%)	15 (13.0)	27 (23.3)	38 (32.8)	0.002
Calcium carbonate, n (%)	3 (2.6)	1 (0.8)	4 (3.4)	0.46
Vitamin D, n (%)	4 (3.5)	5 (4.3)	5 (4.3)	1.00

Data are expressed as medians (interquartile ranges) or as number (percentages) or as means ± SD.
ACI, abdominal aortic calcification index; eGFR, estimated glomerular filtration rate.
LDL-C, low-density lipoprotein cholesterol; PTH, parathyroid hormone.
ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotension receptor blocker.

events were observed. Fig. 2 shows the event-free survival curve for CV outcomes. Kaplan–Meier analysis showed that patients with AAC (ACI > 0) tended to have higher risk of CV outcomes than those without AAC (ACI = 0) (86.5% and 94.4%, $p = 0.12$, respectively) (Fig. 2A). Furthermore, patients in the highest tertile of ACI had the highest risk of CV outcomes compared with the other two groups (96.5%, 93.0%, and 74.3%, p for trend < 0.001, respectively) (Fig. 2B). Data for all clinical events are listed in Supplementary Table 2. There were no significant differences among the three groups in terms of the incidence of non-CV death. However, the incidences of CV death, myocardial infarction, and coronary revascularization in the highest ACI group were significantly higher compared with the other two groups. The incidence of stroke and heart failure in the highest ACI group tended to be higher compared with the other two groups, but did not reach statistical significance. As a result, the rate of composite of adverse CV events in the highest ACI group was numerically higher than that of the other two groups. The results of the Cox proportional hazards models are shown in Table 2. The ACI values and eGFR levels were independently associated with CV outcomes among the asymptomatic patients with CKD [hazard ratio (HR) 1.36, 95% confidence interval (CI) 1.17–1.60, $p < 0.001$ and HR 0.75, 95% CI 0.60–0.93, $p = 0.009$, respectively].

In the ROC analysis, the optimal cut-off value of ACI for the prediction of CV outcomes was 16.2% (sensitivity 78.8%, specificity

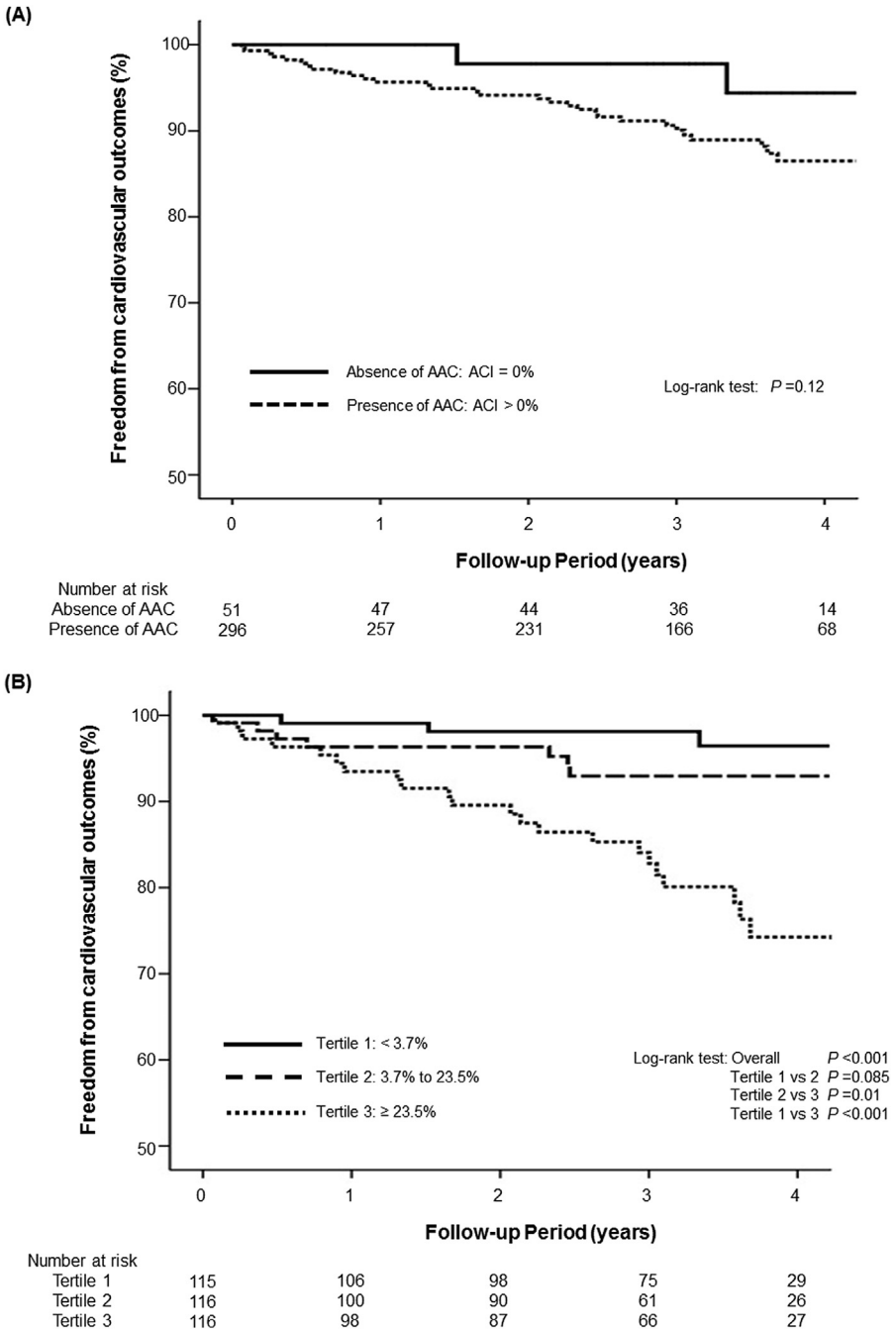


Fig. 2. (A) Event-free survival curve for cardiovascular (CV) outcomes according to the presence or absence of abdominal aortic calcification (AAC). (B) Event-free survival curve for CV outcomes according to the tertiles of aortic calcification index (ACI).

Table 2
Cox regression analysis for prediction of CV outcomes.

Variables	Univariate			Multivariate		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Male	2.06	0.85–4.98	0.11			
Age	1.03	0.99–1.06	0.11			
Body mass index	1.06	0.97–1.16	0.18			
Current Smoking	2.19	0.95–5.04	0.067			
Systolic blood pressure (per 10 mmHg increase)	1.22	1.03–1.45	0.02	1.08	0.89–1.31	0.42
Diabetes	1.64	0.83–3.26	0.16			
Dyslipidemia	1.06	0.48–2.36	0.89			
eGFR (per 10 ml/min/1.73 m^2 increase)	0.75	0.62–0.91	0.004	0.75	0.60–0.93	0.009
Phosphorus	0.99	0.93–1.05	0.69			
Corrected calcium	0.97	0.90–1.06	0.52			
Intact PTH > 65 pg/mL	1.67	0.76–3.65	0.20			
Hemoglobin	0.96	0.81–1.15	0.68			
Albumin (per 0.1 g/dL increase)	0.92	0.87–0.98	0.006	0.99	0.91–1.07	0.75
ACI (per 10% increase)	1.40	1.22–1.61	<0.001	1.36	1.17–1.60	<0.001

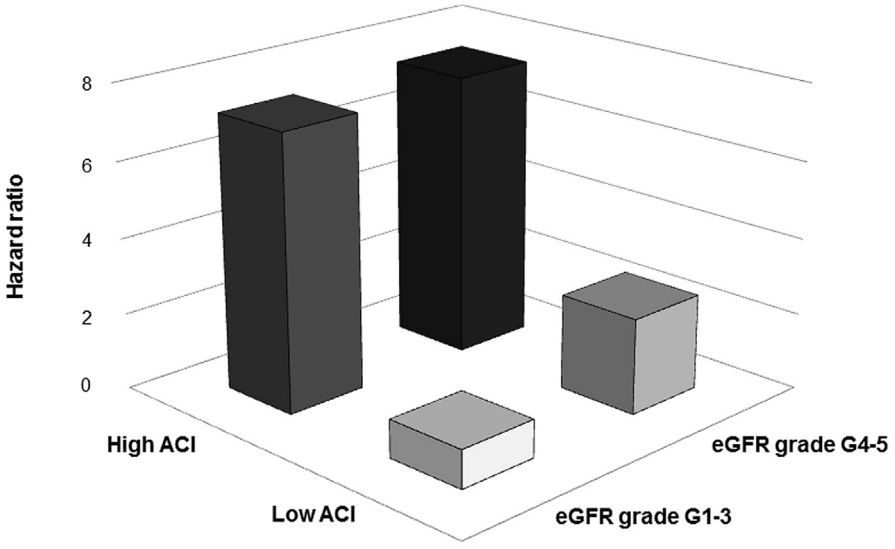
Multivariate model includes all variables at baseline with p < 0.05 by univariate analysis.
CV, cardiovascular; HR, hazard ratio; CI, confidence interval. Other abbreviations as in Table 1.

62.4%, area under the curve = 0.72, $p < 0.001$). The C-index for the prediction of CV outcomes significantly increased when the eGFR and ACI values were added to the model along with the other CV risk factors (0.79 versus 0.66, $p = 0.043$). We also estimated the combined effects of the baseline ACI values (divided by an optimal cut-off value of 16.2%) and eGFR grades (G1–3 or G4–5) for predicting CV outcomes (Fig. 3). After adjusting for conventional CV risk factors including age, gender, BMI, current smoking, SBP, and DM, the HRs (95% CI) of the CV outcomes were 7.25 (2.16–24.29), 2.51 (0.45–14.09), and 7.44 (2.02–27.41) for those with high ACI and G1–3, low ACI and G4–5, and high ACI and G4–5, respectively.

4. Discussion

The main finding of the present study is that high ACI is strongly associated with adverse CV outcomes, even in CKD patients without hemodialysis. From the viewpoint of risk stratification in clinical practice, our findings indicate the considerable significance for asymptomatic CKD patients without hemodialysis, since measurement of ACI by CT scan is a non-invasive and useful screening tool for predicting adverse CV events.

It is widely recognized that the risk for CVD exponentially increases according to the progression of CKD, especially stage 3 and



Category	HR	95% CI	*P* Value
eGFR grade G1-3 and low ACI (n = 164)	(Reference)		
eGFR grade G1-3 and high ACI (n = 92)	7.25	2.16–24.29	0.001
eGFR grade G4-5 and low ACI (n = 39)	2.51	0.45–14.09	0.30
eGFR grade G4-5 and high ACI (n = 52)	7.44	2.02–27.41	0.003

Fig. 3. Combined effects of baseline aortic calcification index (ACI) values (divided by an optimal cutoff value of 16.2%) and eGFR grades (G1–3 or G4–5) for predicting cardiovascular (CV) outcomes. The model was adjusted for conventional CV risk factors, including age, gender, body mass index, current smoking, systolic blood pressure, and diabetes mellitus. Abbreviations as in Tables 1 and 2

higher [1,4,14]. In addition, a recent study reported that elevated serum phosphorus levels, which are a risk factor for death and CV events, are significantly associated with vascular calcification in patients with CKD stages 3–4 [19]. Thus, the KDIGO guidelines recommended the detection and monitoring of laboratory, bone, and CV abnormalities in patients with CKD stages 3–5 [14]. However, it is difficult that we exactly grasp the CKD-MBD condition of each patient, since it presents various conditions according to the differences of patient's background such as aging and diabetes. As a result of our combined analysis, subjects with high ACI in CKD stages 1–3 had a 7.3-fold higher risk for CV outcomes than those with low ACI. These results suggest that assessments of AAC in addition to renal function are needed to improve our ability to identify patients at high risk of CV events and to initiate appropriate preventive measures earlier.

Many cross-sectional and prospective studies have reported the value of AAC for identifying patients at high risk of adverse CV events, including stroke, myocardial infarction, and heart failure [12,13,20,21]. However, the mechanisms underlying the relationship between AAC and CV disease are still unclear. One possible mechanism is that reduced aortic compliance increases left ventricular afterload, which causes left ventricular hypertrophy and heart failure [22–25]. Another possible mechanism may be that both vascular beds (abdominal aorta and coronary arteries) are exposed to the same risk factors for atherosclerosis, including age, smoking, diabetes, and hypertension. Several studies have shown significant association between AAC and coronary atherosclerosis [26,27]. However, even after adjustment for these factors, our data showed that the presence of AAC remained strongly associated with CV outcomes. Furthermore, these relationships were clearly supported by the finding that the model with both ACI and eGFR levels could more accurately predict cardiovascular mortality with an increased C-index. Therefore, all of these patients should be performed non-contrast CT scan to evaluate the severity of AAC, and to improve the predictive ability for future CV events in the asymptomatic CKD patients.

The concept of CKD-mineral and bone disorder (CKD-MBD) was proposed by Kidney Disease Improving Global Outcomes (KDIGO) CKD-MBD Work Group in 2009. Three major components of CKD-MBD consist of mineral and bone laboratory abnormalities, bone abnormality, and vascular calcification [28]. The severity of vascular calcification was thought to be associated not only with the imbalance of calcium, phosphorus, and PTH but also with abnormalities of various calcium-regulatory factors in patients with CKD [29]. A number of studies have reported that these pathophysiological abnormalities have already started in early-stage of CKD [30]. For example, the levels of fibroblast growth factor 23 (FGF23), which regulates phosphorus and vitamin D metabolism, have been reported to be elevated even in patients with early-stage CKD to maintain serum phosphorus levels within the reference range, and has been associated with vascular calcification [19,30–32]. Several epidemiologic studies have reported a significant positive relationship between higher FGF23 levels and the risk of developing CVD as well as CKD progression [33,34]. However the direct mechanism of FGF23 to vascular calcification is still unclear. In the present study, neither serum calcium nor phosphorus levels were independent risk factors for CV outcomes, although the serum intact PTH levels showed a tendency for association with CV outcomes in univariate analysis. Unfortunately, because we did not have the opportunity to measure FGF23 and other important biomarkers related to vascular calcification during the early CKD phase, any association between the severity of the vascular calcification and these biomarkers could not be determined in the present study. To improve the prognosis of the CKD patients, further investigation is therefore needed.

There are some limitations to the present study. First, this study was conducted in a single center and included a relatively small sample. Second, the evaluation using multi-slice CT did not allow distinctions between intimal and medial vascular calcification. Third, we did not compare the semi-quantitative method using non-contrast CT scan with previous qualitative methods, such as plain X-ray films. As for the diagnostic accuracy and detecting vascular calcification in the early phase, CT scan is better than the X-ray methods. However, we must also consider the radiation exposure. Fourth, some specific drugs such as statins and renin-angiotensin system inhibitors have pleiotropic effects including anti-inflammatory and anti-remodeling actions. Basically, such medications were more likely prescribed to patients with multiple risk factors. From these points, medication data should be interpreted. Finally, other CKD-MBD factors that may be associated with vascular calcification in patients with CKD, for example, serum FGF23, were not measured in the present study. Thus, the study limitations should be taken into account when considering the results.

In conclusion, severe AAC was strongly associated with future CV events in asymptomatic CKD patients without hemodialysis. The addition of ACI to the model along with traditional CV risk factors significantly improves the predictive ability for future CV events. These data reinforce the utility of ACI as a useful screening tool in clinical practice.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2015.10.016.

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