



Aortic valve and aortic root calcifications for predicting major adverse cardiovascular events: NADESICO study

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Abstract

To assess aortic valve calcification (AVC) and aortic root calcification (ARC) and to examine their usefulness for predicting major adverse cardiovascular events (MACE). This multicenter prospective cohort study recruited 1187 patients suspected of coronary artery disease (CAD) who underwent coronary computed tomography. MACE included cardiovascular death, myocardial infarction, stroke, revascularization and hospitalization for unstable angina, heart failure or aortic disease. Cox proportional hazard model and C-statistic were used to assess mutual associations between Framingham risk score, coronary artery calcification (CAC) and AVC or ARC with incident MACE. A total of 980 patients (mean age, 65 ± 7 years; female, 45.8%) with assessment of AVC and ARC Agatston scores were analyzed. Among them, 86 developed MACE during a median follow-up of 4.04 years. Cox proportional hazard analyses showed that the presence or severity of AVC and ARC was significantly associated with MACE development after adjusting the CAC Agatston score. Compared with the model of Framingham risk score alone, C-statistics of the model adding AVC or ARC Agatston score to Framingham risk score increased (Δ C-statistic; +0.013 or +0.032, respectively). However, they were not superior to the model adding CAC Agatston (Δ C-statistic; – 0.077 and – 0.058, respectively). AVC or ARC on the top of CAC was a predictive factor for increased MACE in patients with suspected CAD. However, an additional model of AVC or ARC score to Framingham risk score was not as effective as that of CAC Agatston score.

Keywords Aortic valve calcification · Aortic root calcification · Major adverse cardiovascular events · Coronary artery calcification

Abbreviations

ARC	Aortic root calcification
AVC	Aortic valve calcification
AS	Aortic stenosis
BMI	Body mass index
BP	Blood pressure
CAC	Coronary artery calcification
CAD	Coronary artery disease
CAS	Coronary artery stenosis
CCT	Cardiac computed tomography
CI	Confidence interval
CVD	Cardiovascular disease

eGFR	Estimated glomerular filtration rate
FRS	Framingham risk score
HR	Hazard ratio
MACE	Major adverse cardiovascular events
OR	Odds ratio

Introduction

Coronary artery calcification (CAC) assessed using non-contrast cardiac computed tomography (CCT) has been reported to be a coronary atherosclerosis marker and to reflect the total atherosclerosis burden [1, 2]. CAC predicted coronary artery disease (CAD), with high specificity for Agatston score of > 310–400 [3]. Incremental prognostic values were also provided beyond those of traditional cardiovascular risk factors for cardiovascular disease (CVD) morbidity and mortality and helped reclassify patients at risk [4].

During the CCT assessment of patients highly at risk, concomitant aortic valve calcification (AVC) or aortic root

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calcification (ARC) are frequently observed. AVC is a characteristic of aortic stenosis (AS) and shares some cardiovascular risk factors with CAD [5]. Furthermore, it was reportedly assessed by CCT and the Agatston method, and associated with coronary plaque burden and CAD severity [6, 7]. Moreover, aortic calcium is an established marker of atherosclerosis [8]. Consistent with CAC, the prevalence of thoracic aortic calcification including ARC increased with age, was associated with coronary risk factors, and was correlated closely with CAC [9]. Several reports suggested that AVC and ARC predicted CVD events; however, conflicting results regarding its prognostic values in association with cardiovascular risk factors and CAC were also reported [10–12]. The association was a still debate topic. Therefore, we assessed the detailed relationship of AVC or ARC with CAC and examined their usefulness for predicting major adverse cardiovascular events (MACE) in patients suspected of CAD who underwent cardiac CT. Especially, we clarified whether they showed significant predictive values on the top CAC or conventional cardiovascular risk factor model such as Framingham risk scores (FRS).

Materials and methods

Study design

This was a sub-study of the Nationwide Gender-Specific Atherosclerosis Determinants Estimation and Ischemic Cardiovascular Disease Prospective Cohort (NADESICO) study, a prospective, multicenter cohort designed to evaluate the sex difference in the association of coronary atherosclerosis including CAC with MACE [13]. Our study protocol was registered with the UMIN Clinical Trials Registry (UMIN-CTR ID: UMIN000001577) before data were released to the lead author. The protocol and informed consent were approved by the institutional review board of each center including the National Cerebral and Cardiovascular Center (M20-029-7), and written informed consent was obtained from each patient before participation.

Participants

Patients included in this study were enrolled from the cardiology department of each hospital participating in the NADESICO study and were recruited from December 2008 to April 2013 among 15 hospitals in Japan. The inclusion criteria were as follows: (1) 50–74-year-old patients suspected with CAD in a stable setting, who had adequate indications for plain CT and coronary CT angiography and (2) patients without a history of myocardial infarction or coronary artery revascularization. Patients who fulfilled the following criteria were excluded: (1) patients with a history

of Kawasaki disease, (2) coronary artery malformation, (3) familial hypercholesterolemia, (4) limited prognosis due to malignant tumors, (5) on dialysis, or (6) under treatment for a serious mental or neurological disorder.

Data collection

Clinical data of diagnostic and therapeutic measures were collected by investigators at each hospital and sent to National Cerebral and Cardiovascular Center. Hypertension was defined as systolic blood pressure (BP) of ≥ 140 mmHg or diastolic BP of ≥ 90 mmHg, or current use of antihypertensive agents. Diabetes mellitus was defined as an adult-onset self-reported history, fasting glucose level of ≥ 126 mg/dl, or usage of insulin or oral glucose-lowering medications. Dyslipidemia was defined as the current usage of any lipid-lowering agents, triglyceride level of ≥ 150 mg/dl, low-density lipoprotein cholesterol of ≥ 140 mg/dl, or high-density lipoprotein cholesterol of ≤ 40 mg/dl in male and ≤ 50 mg/dl in female. Data on smoking habits and medical history were collected using a questionnaire at enrollment. Laboratory examination included complete blood count, lipid profiles and fasting plasma glucose levels.

CT was performed using ≥ 64 channels with electrocardiography gating following the guidelines from the Japanese Circulation Society and institutional protocols. CT imaging was transferred to National Cerebral and Cardiovascular Center through digital imaging and interpreted in a blinded fashion with an independent imaging core laboratory using SYNAPSE VINCENT[®] (FUJIFILM Medical Co., Ltd., Tokyo, Japan). An experienced radiologist or cardiologist blinded to all clinical data interpreted plain CT scans with CAC, AVC, and ARC scores using the Agatston method. AVC was measured in the aortic valve leaflets and annular calcification [11]. ARC was measured in the part of the aorta lying within 3 cm of the aortic annulus involving the Valsalva sinuses and sinotubular junction, except for AVC [12].

Follow-up

Follow-up was conducted annually from enrollment until March 2020. The attending physician from each hospital checked the presence or absence of MACE. For patients who did not visit the hospital more than once a year, the attending physician of each hospital contacted the patients every year by telephone or mail. MACE was defined as the composite of cardiovascular death, myocardial infarction, stroke, revascularization, and hospitalization for unstable angina, heart failure or aortic disease. Cardiovascular death was defined as death due to myocardial infarction, heart failure, cardiac arrhythmia, sudden cardiac death, aortic disease, and stroke.

Statistical analysis

Continuous data were presented as mean \pm standard deviation and categorical data were displayed as a number (%). One-way analysis of variance and chi-squared tests were used to test significant differences between three groups (according to AVC or ARC severity) for continuous and categorical variables, respectively. The relationship between CAC severity (no CAC: CAC Agatston score = 0, mild CAC: $0 < \text{CAC Agatston score} < 100$; moderate CAC: $100 \leq \text{CAC Agatston score} < 400$; severe CAC: $400 \leq \text{CAC Agatston score}$) and AVC or ARC severity (No: Agatston score = 0, mild: $0 < \text{Agatston score} < \text{the 90th percentile value}$; and severe: $\text{the 90th percentile value} \leq \text{Agatston score}$) were examined by Cochran–Armitage test. The cut-off level of AVC or ARC severity as 90th percentile value was exploratory determined considering the distribution of AVC or ARC Agatston score in this study. The logistic regression model was used to identify CV risk factors associated with the presence (Agatston score > 0) of AVC or ARC or CAC. Kaplan–Meier analysis was used to examine the incidence of MACE based on AVC or ARC severity. The Cox proportional hazard model for MACE was adjusted by age and/or CAC Agatston score. Harrell's concordance statistic (C-statistic) for predicting MACE was examined by adding AVC and ARC Agatston score (continuous value) to calculated Framingham risk score directly [14] and/or CAC of each patient. This analysis was conducted in overall group and male/female groups. The 95% confidence intervals of C-statistic were estimated using 200 bootstrap samples. Statistical significance was defined as a two-tailed *P* value of < 0.05 . In the analysis of reclassification of Framingham risk score after addition of CAC, AVC or ARC Agatston score, low risk was determined as a risk of $< 6\%$, intermediate risk was 6–20% and high risk was $> 20\%$. Also, Kaplan–Meier analysis and Cox proportional hazard model for MACE adjusted by age and/or CAC Agatston score were also examined using another criteria of

AVC or ARC severity according to Agatston score (Agatston score = 0, $0 < \text{Agatston score} < 100$, $100 \leq \text{Agatston score}$) based on previous study in addition to the severity classified by 90th percentile value [15]. Statistical analyses were performed using Stata 17 (StataCorp, College Station, TX, USA).

Results

Cardiovascular risk factors associated with AVC or ARC

A total of 980 patients (mean age, 65 ± 7 years) who were suspected with CAD and available for Agatston score of aortic valve, aortic root and coronary artery were investigated (Supplementary Fig. 1), which comprised 449 (45.8%) females. Patients with severe AVC or severe ARC were older and had hypertension, diabetes mellitus, chronic kidney disease, dyslipidemia, and current or past smoking more frequently (Supplementary Table 1). Multivariable analysis showed advanced age, hypertension, and dyslipidemia were independently associated with AVC, whereas advanced age, diabetes mellitus, dyslipidemia, and current or past smoking habits were independently associated with ARC (Table 1). In contrast, all risk factors except for body mass index ≥ 25 and chronic kidney disease were associated with CAC.

Association of AVC and ARC with MACE

The distribution of Agatston scores in AVC and ARC is shown in Supplementary Fig. 2. The median AVC Agatston score was 0 (interquartile range [IQR]: 0–8.25), with the 90 percentile of 76.45. The median ARC Agatston score was 0 (IQR: 0–25.8), with the 90 percentile of 174.75. Kaplan–Meier analysis for MACE showed that incidences of MACE in patients with severe AVC and

Table 1 Multivariable analysis for baseline cardiovascular risk factors associated with the calcifications

	Aortic valve calcification			Aortic root calcification			Coronary artery calcification		
	OR	95% CI	<i>P</i> value	OR	95% CI	<i>P</i> value	OR	95% CI	<i>P</i> value
Age (/ + 1 year old)	1.10	1.07–1.13	< 0.01	1.11	1.08–1.14	< 0.01	1.09	1.07–1.12	< 0.01
Male	0.96	0.66–1.40	0.84	0.84	0.58–1.20	0.33	2.48	1.72–3.59	< 0.01
BMI ≥ 25	1.02	0.74–1.39	0.91	1.04	0.77–1.41	0.79	1.18	0.84–1.64	0.34
Hypertension	1.73	1.26–2.37	< 0.01	1.31	0.97–1.76	0.08	2.08	1.54–2.82	< 0.01
Diabetes mellitus	1.17	0.84–1.62	0.36	1.88	1.37–2.60	< 0.01	1.72	1.17–2.52	< 0.01
Dyslipidemia	1.43	1.07–1.93	0.02	1.46	1.10–1.95	< 0.01	1.45	1.07–1.97	0.02
Current or past smoking	1.34	0.92–1.96	0.13	2.21	1.53–3.19	< 0.01	1.54	1.06–2.22	0.02
Chronic kidney disease	1.23	0.83–1.82	0.30	1.12	0.75–1.65	0.58	1.09	0.68–1.74	0.71

OR was adjusted by all of the above factors

BMI body mass index, CI confidence interval, OR odds ratio

ARC were higher than those without (Fig. 1). The Cox proportional hazard model adjusted by age and sex (Model 1, Table 2) showed that the presence and severity of AVC and ARC were significantly associated with increased occurrence of MACE.

Association of AVC, ARC and CAC with MACE

Figure 2 shows that the severity of AVC or ARC was associated with that of CAC based on the Agatston score ($P < 0.01$, respectively). The Cox proportional hazard model adjusted by age, sex, and CAC Agatston score (Model 2, Table 2)

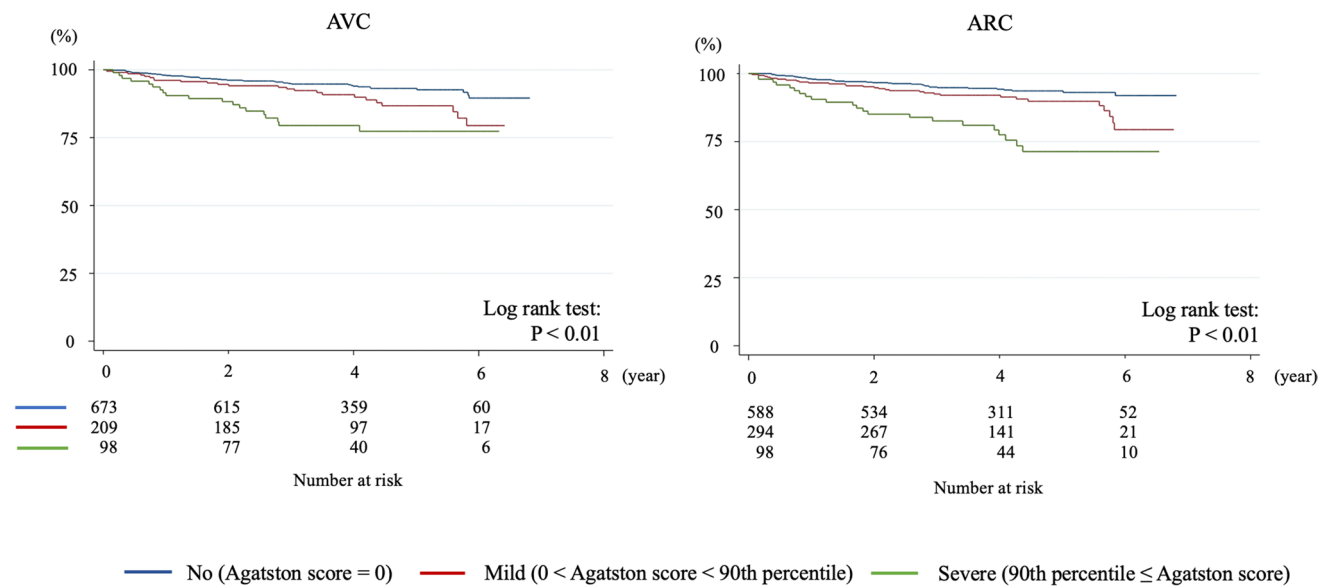


Fig. 1 Kaplan–Meier analysis for MACE stratified by AVC or ARC severity. Blue line indicates no calcification (Agatston score 0), red line indicates mild calcification (0 < Agatston score < 90th percentile), and green line indicates severe calcification (90th percentile ≤ Agatston score). ARC aortic root calcification, AVC aortic valve calcification, MACE major adverse cardiovascular event

tile), and green line indicates severe calcification (90th percentile ≤ Agatston score). ARC aortic root calcification, AVC aortic valve calcification, MACE major adverse cardiovascular event

Table 2 Cox proportional hazard model of AVC and ARC for MACE

	Model 1			Model 2		
	HR	95% CI	P value	HR	95% CI	P value
Aortic valve calcification (AVC)						
Absence or presence of AVC						
Absence of AVC (Agatston score = 0)	1	(Reference)		1	(Reference)	
Presence of AVC (Agatston score > 0)	2.26	1.46–3.50	< 0.01	1.78	1.13–2.82	0.01
AVC severity						
No AVC (Agatston score = 0)	1	(Reference)		1	(Reference)	
Mild AVC (0 < Agatston score < 90 percentile)	1.84	1.10–3.06	0.02	1.44	0.85–2.44	0.17
Severe AVC (90 percentile ≤ Agatston score)	3.31	1.88–5.85	< 0.01	2.66	1.48–4.77	< 0.01
Aortic root calcification (ARC)						
Absence or presence of ARC						
Absence of ARC (Agatston score = 0)	1	(Reference)		1	(Reference)	
Presence of ARC (Agatston score > 0)	2.21	1.42–3.44	< 0.01	2.04	1.30–3.19	< 0.01
ARC severity						
No ARC (Agatston score = 0)	1	(Reference)		1	(Reference)	
Mild ARC (0 < Agatston score < 90 percentile)	1.70	1.03–2.80	0.04	1.71	1.04–2.82	0.04
Severe ARC (90 percentile ≤ Agatston score)	3.90	2.24–6.78	< 0.01	2.93	1.64–5.23	< 0.01

Model 1, HR was adjusted by age and sex; Model 2, HR was adjusted by age, sex, and CAC Agatston score

ARC aortic root calcification, AVC aortic valve calcification, CI confidence interval, HR hazard ratio, MACE major adverse cardiovascular event

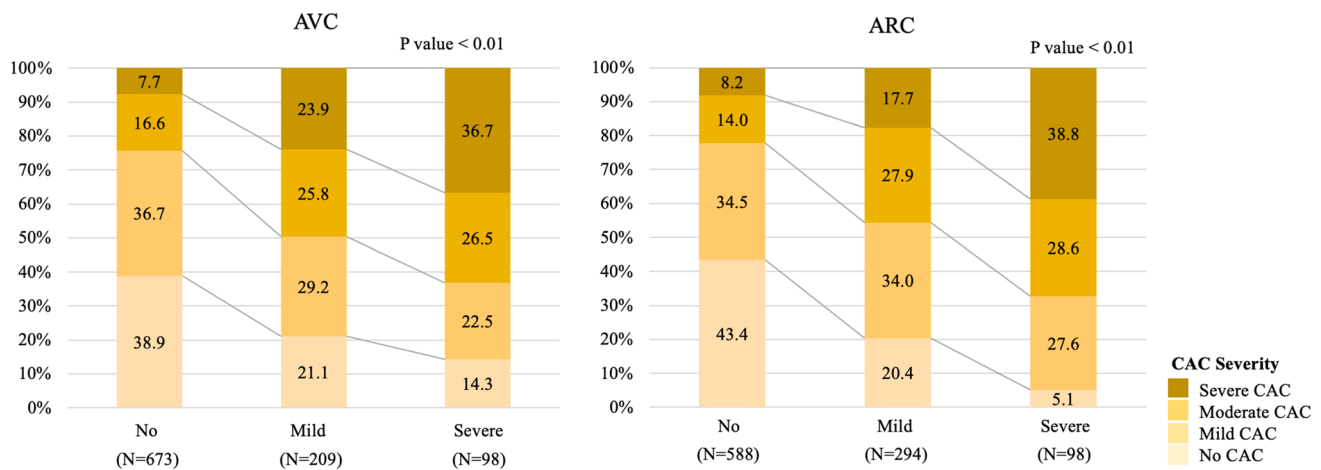


Fig. 2 The relationship between CAC and AVC or ARC according to calcification severity. AVC and ARC; No: Agatston score = 0, Mild: $0 < \text{Agatston score} < 90^{\text{th}}$ percentile, Severe: 90^{th} percentile \leq Agatston score. CAC; No CAC: CAC Agatston score = 0, Mild

CAC: $0 < \text{CAC Agatston score} < 100$, Moderate CAC: $100 \leq \text{CAC Agatston score} < 400$, Severe CAC: $400 \leq \text{CAC Agatston score}$. ARC aortic root calcification, AVC aortic valve calcification, CAC coronary artery calcification

showed that the presence and severe AVC and the presence, mild, and severe ARC were associated with increased occurrence of MACE. In all patients, the C-statistics were significantly increased by adding ARC assessment to Framingham risk score model (Δ C-statistic; +0.032, $P = 0.01$), not significant by adding AVC (Δ C-statistic; +0.013, $P = 0.06$) compared with Framingham risk score alone (Table 3). However, C-statistic in combined models adding AVC or ARC Agatston score to Framingham risk score model was significantly lower than that in model of adding CAC Agatston score to Framingham risk score model (Δ C-statistic; -0.077 , $P < 0.01$, or Δ C-statistic; -0.058 , $P < 0.01$, respectively). Additional assessment of AVC, ARC, or CAC Agatston score to Framingham risk score led to a net increase of 1, 5, or 9% in patients with MACE, and 1, 3, or 23% in patients without MACE correctly reclassified (net reclassification index, 0.25 ± 0.11 , 0.38 ± 0.11 , or 0.72 ± 0.11 , respectively) (Supplementary Fig. 3). When

compared to the combined model with Framingham risk score and CAC Agatston score, additional assessment of AVC and ARC Agatston scores led to a net increase of 5% in patients with MACE and 5% in patients without MACE correctly reclassified (net reclassification index, 0.32 ± 0.11), although C-statistic did not significantly increase.

Sex difference in AVC and ARC

During a follow-up period, 65 male and 21 female patients developed MACE. In contrast to CAC, AVC, and ARC were not independently associated with gender (Table 1). In the stratified analysis by gender, differences were observed in cardiovascular risk factors associated with AVC and ARC (Supplementary Table 2). Age and dyslipidemia were associated with AVC in male, whereas age and hypertension in female. Conversely, age, diabetes mellitus, dyslipidemia, and smoking were associated with ARC in male and all these

Table 3 Harrell's concordance statistics for MACE

	C-statistic	95% low CI	95% upper CI	Δ C-statistic	P value	Δ C-statistic	P value
FRS	0.615	0.555	0.675	Reference	–		
FRS + CAC	0.705	0.641	0.769	0.091	<0.01	Reference	–
FRS + AVC	0.628	0.567	0.688	0.013	0.06	-0.077	<0.01
FRS + ARC	0.647	0.585	0.709	0.032	0.01	-0.058	<0.01
FRS + CAC + AVC	0.706	0.641	0.770	0.091	<0.01	0.001	0.83
FRS + CAC + ARC	0.707	0.643	0.771	0.093	<0.01	0.002	0.61
FRS + AVC + ARC	0.650	0.588	0.712	0.035	<0.01	-0.055	<0.01
FRS + CAC + AVC + ARC	0.708	0.644	0.772	0.093	<0.01	0.003	0.51

ARC aortic root calcification, AVC aortic valve calcification, CAC coronary artery calcification, CI confidence interval, FRS Framingham risk score calculated directly, MACE major adverse cardiovascular event

factors except for dyslipidemia in female. AVC and ARC severities were similarly associated with CAC severity in both sexes (Supplementary Fig. 4). Although MACE was lesser in female than in male, no differences were observed in the relationship of AVC or ARC with MACE between sexes (Supplementary Figs. 5 and 6). In male, C-statistic in the model adding CAC or ARC Agatston score to Framingham risk score significantly increased (Δ C-statistic; +0.070, $P < 0.01$, or Δ C-statistics; +0.035, $P = 0.049$, respectively, Supplementary Table 3). In female, C-statistic in the model adding CAC, AVC and ARC Agatston score to Framingham risk score significantly increased compared with Framingham risk score alone model (Δ C-statistic; +0.056, $P = 0.045$).

Another grading of AVC, ARC using Agatston score 100

Of patients with AVC or ARC, 227 patients had ' $0 < \text{AVC Agatston score} < 100$ ' and 80 patients had ' $100 \leq \text{AVC Agatston score}$ ', and 257 patients had ' $0 < \text{ARC Agatston score} < 100$ ', 135 patients had ' $100 \leq \text{ARC Agatston score}$ '. Kaplan–Meier analysis for MACE showed that incidence of MACE in patients with AVC or ARC with ' $100 \leq \text{Agatston score}$ ' was highest (Supplementary Fig. 7). Cox proportional hazard model adjusted by age, sex, and CAC Agatston score showed that AVC or ARC with ' $100 \leq \text{Agatston score}$ ' was associated with increased incidence of MACE (Supplementary Table 4).

Discussion

Different pathogenesis between AVC and ARC

Extracoronary calcifications, AVC and ARC, were associated with cardiovascular risk factors differently. Hypertension was strongly associated with AVC, whereas diabetes mellitus and current or past smoking were associated with ARC in this study, suggesting that the formation mechanism may be different between AVC and ARC. Although AVC is a characteristic feature of AS and is not usually considered part of the atherosclerotic process, shared pathological mechanisms of the heart valve calcification and coronary atherosclerosis have been discussed [16]. Hypertension was independently associated with AVC, reflecting age-related degenerative calcification and contribution of mechanical stress through the blood flow [17–20]. Although chronic kidney disease has also been previously known as a strong factor for AVC formation [19], no significant relationship was observed in our study. This may be explained by including the small number of patients with chronic kidney disease in this NADESICO study. Moreover, aortic calcium is an

established marker of atherosclerosis [8]. Consistent with CAC, the prevalence of thoracic aortic calcification including ARC increased with age, was associated with coronary risk factors, and was closely correlated with CAC [21, 22]. Especially, the aortic root has been characterized by its close anatomical proximity to the cardiac chambers and ostium of coronary arteries [10, 20].

AVC and ARC as predictive factors

In this study, the presence of AVC and ARC, especially with higher Agatston scores, was associated with MACE development in patients suspected of CAD. AVC has been reportedly associated with mortality in patients with AS, and the partial association of AVC and ARC with MACE has been previously suggested in the younger population [23–25]. Since these results analyzed with AVC and ARC severity using 90th percentile values (AVC 76.45 and ARC 174.75) were almost compatible with those with other categorical severity using Agatston score 100, setting the cut-off points of AVC or ARC around 100 seemed to be useful to predict incidence of MACE in patients with suspicious of CAD and without severe AS. This study was unique due to its usefulness of AVC, and ARC Agatston scores were examined by analyzing C-statistic with the combination of traditional Framingham risk score and CAC Agatston score. Models adding AVC or ARC Agatston scores to Framingham risk score were useful to predict for MACE; however, its usefulness was not superior to the model adding CAC Agatston score. This supports that CAC, based on its representation of the total atherosclerosis burden directly within the coronary arteries, remains a stronger predictor.

Sex differences in AVC and ARC

Factors associated with AVC and ARC seemed to be slightly different in analyzing each sex group. In this study, associations of hypertension and dyslipidemia with both AVC and ARC were observed in female and male, respectively. Erbel et al. reported that female with AVC tended to be accompanied by left ventricular hypertrophy, which may imply its association with HT [26]. Furthermore, AVC was reported to be mainly detected as the aortic valve degeneration in male and fibrosis in female. The etiology and formation of AVC and ARC may vary in sex; however, no difference was observed in the susceptibility of calcification. Moreover, the resulting calcification was associated with clinical outcomes without showing sex differences. This result was in contrast with that in CAC, which was more frequently observed in male by 2.48 times. In the analysis of C-statistic, additional assessment of CAC Agatston score in male and all CAC, AVC and ARC Agatston scores in female to Framingham risk score seemed to be most useful to predict MACE.

Pressman et al. recently advanced the notion of “total cardiac calcium” as a predictor of cardiovascular risk [27], and sex difference may be also existed in the notion [28, 29]. However, the sex differences in cardiovascular calcifications are still controversial, and further studies in a larger and broad-spectrum cohort will be needed to clarify differences between the CAC and AVC or ARC based on sex differences.

Limitation

This study has several limitations. First, a small number of MACE occurrences may affect the result, especially in females. Previous studies have reported a similar relatively low incidence of MACE in patients suspected with CAD in Japan [30]. Information regarding medications during follow-up was not obtained and incorporated into the analysis. Second, AS is associated with AVC and one of the important factors which affect the incidence of MACE through angina or heart failure [31]. Most previous studies examined the AVC Agatston score in patients including severe AS [32, 33]. We could not examine the detailed association between AVC and severity of AS because echocardiographic data were not available in the present study. However, based on their medical history records, patients with at least moderate and severe AS were not included in the present study, and the impact of AS on the present findings may be small. Finally, our results from an Asian cohort may not be generalizable to other ethnic groups due to the existence of racial differences in the prevalence and severity of CAC and incidence of CAD [34, 35].

Conclusions

AVC or ARC was associated with specific cardiovascular risk factors and MACE incidence in patients suspected with CAD who underwent cardiac CT. Although AVC or ARC on the top of CAC was a predictive factor for increased MACE, additional effect of AVC or ARC Agatston score to Framingham risk score was modest and the model was not as useful as that of CAC Agatston score.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00380-022-02187-9>.

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Author contributions Study concept and design: SW, YI, and TN; data curation: SW and MN; analysis and interpretation of data: SW, MN, and YI; interpretation of results: YM and TN; supervision: YM and TN; writing—original draft: SW; writing—reviewing and editing: YI.

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Declarations

Conflict of interest The authors have no competing interests to declare.

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