



# Predictive value of abdominal aortic calcification index for mid-term cardiovascular events in patients with acute coronary syndrome

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## Abstract

The utility of abdominal aortic calcification (AAC) for prediction of cardiovascular events (CVEs) in patients with acute coronary syndrome (ACS) remains to be determined. The aim of this prospective study was to determine the predictive value of the abdominal aortic calcification index (ACI), a semi-quantitative measure of AAC, for CVEs in patients with ACS. We evaluated 314 patients with ACS. All patients underwent successful percutaneous coronary intervention to the culprit coronary vessel without in-hospital adverse events. ACI was calculated on non-contrast computed tomography images. CVEs were defined as a composite of cardiovascular death, ACS recurrence, and stroke. During a median follow-up period of 19.1 months, CVEs occurred in 29 patients (9.2%). Multivariable regression analysis after adjustment for age and gender showed a significantly higher baseline ACI in patients with CVEs than in those without [median (interquartile ranges), 42.1 (25.9–60.2) vs. 20.8 (8.8–38.6) %;  $P=0.021$ ]. The cutoff value of ACI for prediction of CVEs, estimated by receiver-operating characteristic analysis, was 29.2%, with sensitivity of 76% and specificity of 64% (area under the curve, 0.69). After adjustment for conventional cardiovascular risk factors, Cox analysis showed high ACI ( $\geq 29.2\%$ ) to be significantly associated with increased risk of CVEs ( $P=0.011$ ; hazard ratio, 1.82). Multivariate analysis identified high ACI as an independent predictor of CVEs ( $P=0.012$ ; hazard ratio, 1.80). Stepwise forward selection procedure also showed that high ACI was a significant independent determinant of CVEs ( $P=0.004$ ;  $R^2$ , 0.089). Both net reclassification improvement (0.64;  $P=0.001$ ) and integrated discrimination improvement (0.04;  $P<0.001$ ) improved significantly after the addition of high ACI to conventional risk factors. Evaluation of ACI using CT seems to provide valuable clinical information for proper assessment of mid-term CVEs in patients with ACS after percutaneous coronary intervention.

**Keywords** Abdominal aortic calcification index · Non-contrast CT scan · Cardiovascular event · Acute coronary syndrome

## Introduction

Acute coronary syndrome (ACS) is an important clinical challenge based on the associated risk of mortality. The development of revascularization procedures and new

medical therapies has improved both the short- and long-term prognoses of such patients [1–4]. However, the rate of secondary cardiovascular events (CVEs) in patients with ACS remains high [1–5]. Thus, risk stratification is important for accurate assessment of long-term prognosis. Previous studies examined the relationship between abdominal aortic calcification (AAC) and CVEs [6–9]. In the majority of these studies, the study subjects were recruited from the general population, and AAC was evaluated by lateral lumbar radiography [7–9]. Given that computed tomography (CT) scan is more sensitive in detecting AAC compared with lumbar radiography, measurement of AAC by CT scan may be more suitable for assessing the risk of CVEs in high-risk patients. Using non-contrast CT scans, we reported previously the utility of the abdominal aortic calcification index (ACI), a semi-quantitative index of AAC, in the prediction

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of CVEs in asymptomatic chronic kidney disease patients not on hemodialysis [10]. However, the exact predictive value of ACI for CVEs in patients with ACS has not been determined definitively. The aim of this study was to determine the predictive value of ACI for CVEs in patients with ACS.

## Materials and methods

### Subjects

We screened 453 consecutive patients with ACS who underwent successful percutaneous coronary intervention (PCI) to the culprit coronary vessel at our hospital between February 2013 and January 2017. ACS included acute MI and unstable angina pectoris. Acute MI was defined as typical acute chest pain associated with myocardial ischemia and abnormal levels of cardiac biomarkers ( $> 99$ th centile of the upper normal limit) [11]. Acute MI was also divided into ST-segment elevation MI (STEMI) and non-ST-segment elevation MI (NSTEMI), based on electrocardiographic findings [12]. Unstable angina pectoris was defined as acute chest pain or worsening chest discomfort with normal cardiac enzyme levels, requiring revascularization. We excluded the subjects with the following conditions: (1) history of in-hospital adverse events, including death, cardiac surgery, cardiac arrest requiring resuscitation, ACS recurrence, or stroke; (2) history of abdominal aortic replacement; (3) presence of other life-threatening diseases; and (4) follow-up period limited to  $\leq 6$  months. Accordingly, a total of 314 patients were evaluated in this study (Supplemental Fig. 1). The study protocol complied with the Declaration of Helsinki and was approved by the local ethics committee (IRB #2017371). Written informed consent was obtained from each participant.

### Measurement of abdominal aortic calcification index

All subjects underwent a 64-slice non-contrast CT scan (Siemens Medical Solutions, Forchheim, Germany) within 2 weeks of PCI. Scanning was performed in the supine position and cranio-caudal direction. 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. Each cross-section image of the abdominal aorta on each slice was divided into 12 radial segments. Calcification was considered to be present if an area of  $> 1 \text{ mm}^2$  displayed a density of  $> 130$  Hounsfield units. The number of calcified segments on each slice was counted. The ACI was calculated using the following equation (Fig. 1) [10, 13, 14]:  $\text{ACI} (\%) = (\text{total score for calcification on all slices}) / (\text{number of}$

$\text{slices} \times 12) \times 100$ . AAC was measured semi-quantitatively and independently by two physicians who were both blinded to the clinical characteristics of the patients. The inter- and intra-observer variabilities of ACI correlated well [ $r = 0.99$  ( $P < 0.001$ ) and  $r = 0.99$  ( $P < 0.001$ ), respectively]. Details of the procedure were described previously [10, 13].

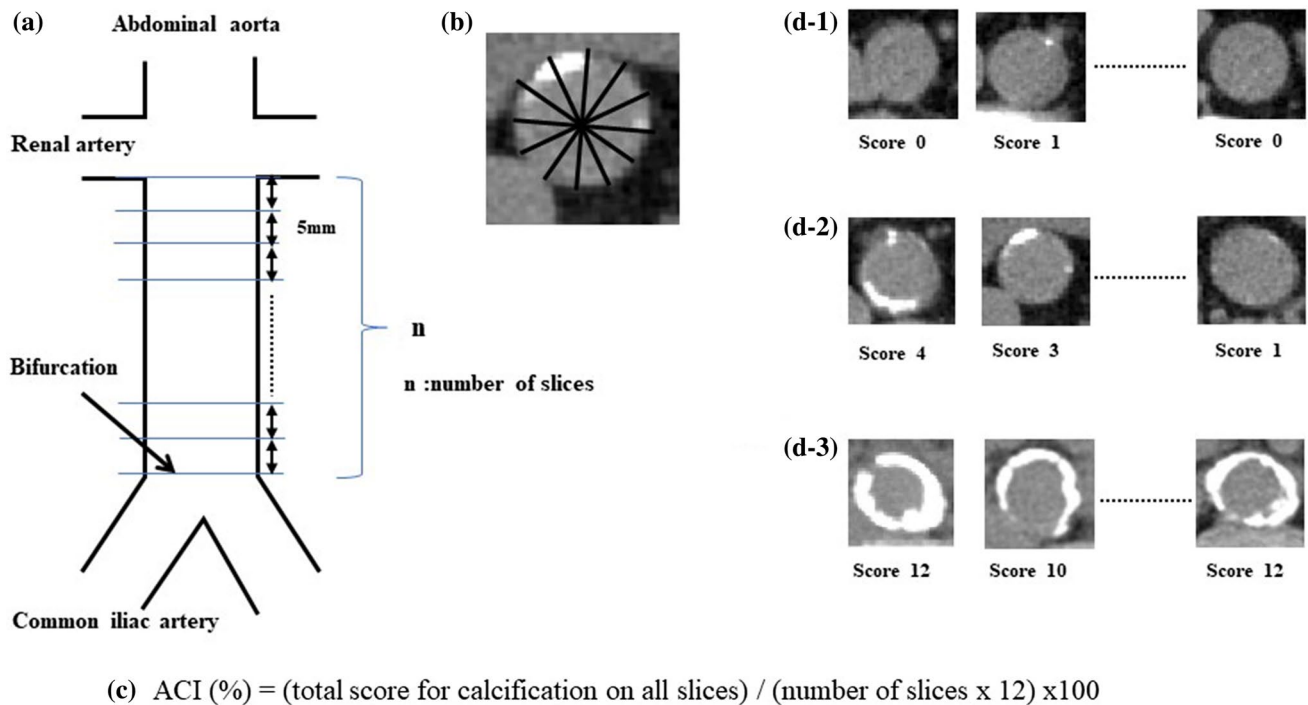
### Data collections

The clinical data of medical history, physical examination, anthropometric measurements, and self-reported questionnaires on lifestyle (e.g., smoking habit) were collected during hospitalization. Left ventricle ejection fraction (LVEF) was measured using transthoracic echocardiography before discharge. Blood pressure was measured at least twice after  $> 5$  min rest in the sitting position before discharge. Venous blood samples (total volume; 10 ml) were also collected in the early morning after overnight fasting before discharge. Fasting plasma glucose level, blood glycosylated hemoglobin content, and serum concentrations of total cholesterol, triglycerides, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, creatinine, and B-type natriuretic peptide (BNP) were measured. The estimated glomerular filtration rate (eGFR) was calculated using a simplified prediction equation derived from that in the Modification of Diet in Renal Disease Study [15] and proposed by the Japanese Society of Nephrology:  $\text{eGFR} (\text{ml/min}/1.73 \text{ m}^2) = 194 \times [\text{age (years)}]^{-0.287} \times [\text{serum creatinine (mg/dl)}]^{-1.094} [\times 0.739 \text{ for females}]$  [16].

Clinical events were collected from the medical records or telephone interview. Follow-up was censored on September 18, 2018. The endpoint of this study was CVE, which was defined as composite of cardiovascular death, ACS recurrence, and stroke. Cardiovascular death was defined as death due to acute MI, sudden cardiac death, heart failure, stroke, cardiovascular procedure, cardiovascular hemorrhage, or other cardiovascular-related causes [12]. When non-cardiac cause of death could not be identified, it was also considered as cardiac death. ACS recurrence was defined as either recurrent acute MI or unstable angina pectoris. Recurrent MI also included a rise in cardiac biomarker values of  $> 5$  or  $> 10$  times above the 99th centile of the upper normal limit in subjects who underwent additional PCI or bypass graft surgery [12]. Stroke included both ischemic and hemorrhagic types, and was defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury as a result of infarction or hemorrhage [12].

### Statistical analysis

Data with normal distribution pattern were expressed as mean  $\pm$  standard deviation, and those with skewed



**Fig. 1** The method used for calculating abdominal aortic calcification index (%). **a** 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 seg-

ments was counted on each slice. **c** This formula was used to calculate the abdominal aortic calcification index (ACI). **d** Representative cross-sectional images of the abdominal aorta in patients with 1.9% (d-1), 42.9% (d-2), and 92.6% ACI (d-3). Details were described by Tatami et al. [10]

distribution were expressed as median values (interquartile ranges). Categorical variables were compared by the Chi square test. Comparisons between two groups were conducted by the unpaired Student's *t* test (for variables with normal distribution) or by Mann–Whitney *U* test (for variables with skewed distribution). ACI was compared between patients with and without CVEs by multivariable regression analysis after adjustment for age and gender. Receiver-operating characteristic curve analysis was performed to determine the optimal cutoff value of ACI for the prediction of CVEs. The event-free survival curve was analyzed using Kaplan–Meier method with log-rank test. The relationship between ACI and CVEs was evaluated by Cox analysis adjusted for conventional cardiovascular risk factors (including age, gender, body mass index, hypertension, dyslipidemia, diabetes, current smoking, and eGFR). Cox proportional hazard model was also performed to identify independent predictors of CVEs. Multivariate analysis included all variables measured at baseline that showed  $P < 0.05$  with CVEs in univariate analysis. Stepwise forward selection analysis was also performed to examine the effects of ACI as well as other covariates ( $P < 0.05$  in Cox univariate analysis) on CVEs. In this analysis, the *P* levels for inclusion in and exclusion from the model were 0.25 and 0.1, respectively. The C-index, net reclassification improvement,

and integrated discrimination improvement were calculated to assess whether the accuracy of predicting CVEs would improve after adding ACI into the base model with other risk factors [17, 18]. The base model consisted of conventional risk factors. Finally, the relationships between ACI and clinical characteristics were examined by linear regression analysis. In addition, Cox analysis was performed to evaluate the association of ACI with CVEs after adjustment for each variable related to ACI ( $P < 0.05$ ).  $P < 0.05$  denoted the presence of a statistically significant difference. Statistical tests were conducted using the JMP software (version 5.1 and 13.0; SAS Institute, Inc., Cary, NC). DeLong test for C-index was examined with sample script ([https://www.jmp.com/japan/support/faq/stat\\_3605.shtml](https://www.jmp.com/japan/support/faq/stat_3605.shtml)).

## Results

The baseline characteristics of the study subjects are summarized in Table 1. The median follow-up period was 19.1 months. During the follow-up period, ACS recurrence was diagnosed in 10 patients (STEMI,  $n = 1$ ; NSTEMI,  $n = 3$ ; unstable angina pectoris,  $n = 6$ ), and stroke in 14 (ischemic stroke,  $n = 10$ ; hemorrhagic stroke,  $n = 4$ ) (Table 2). Nine patients died and the cause of death was

**Table 1** Baseline characteristics of study subjects

Variables	All subjects ( <i>n</i> = 314)	Patients with CVEs ( <i>n</i> = 29)	Patients without CVEs ( <i>n</i> = 285)	<i>P</i> value
Age, years	68 (61–78)	74 (66–84)	67 (61–77)	0.007
Male, <i>n</i> (%)	238 (75.8)	21 (72.4)	217 (76.1)	0.655
Body mass index, kg/m <sup>2</sup>	23.0 (21.0–25.3)	22.5 (19.3–23.6)	23.1 (21.1–25.5)	0.012
Hypertension, <i>n</i> (%)	213 (67.8)	24 (82.8)	189 (66.3)	0.071
Diabetes, <i>n</i> (%)	97 (30.9)	12 (41.4)	85 (29.8)	0.200
Dyslipidemia, <i>n</i> (%)	179 (56.1)	14 (48.3)	162 (56.8)	0.376
Current smoker, <i>n</i> (%)	113 (36.0)	7 (24.1)	106 (37.2)	0.163
Previous myocardial infarction, <i>n</i> (%)	48 (15.3)	7 (24.1)	41 (14.4)	0.164
Previous heart failure, <i>n</i> (%)	34 (10.8)	8 (27.6)	26 (9.1)	0.002
Atrial fibrillation, <i>n</i> (%)	23 (7.3)	2 (6.9)	21 (7.4)	0.926
Classification of acute coronary syndrome				0.026
STEMI, <i>n</i> (%)	207 (65.9)	13 (44.8)	194 (68.1)	
NSTEMI, <i>n</i> (%)	57 (18.2)	10 (34.5)	47 (16.5)	
Unstable angina pectoris, <i>n</i> (%)	50 (15.9)	6 (20.7)	44 (15.4)	
Left main coronary artery lesion, <i>n</i> (%)	17 (5.4)	5 (17.2)	12 (4.2)	0.003
Multi-vessel disease, <i>n</i> (%)	151 (48.1)	17 (58.6)	134 (47.0)	0.234
Culprit artery of acute coronary syndrome				0.042
Left main trunk	9 (2.9)	3 (10.3)	6 (2.1)	
Right coronary artery	124 (39.5)	8 (27.6)	116 (40.7)	
Left anterior descending artery	144 (45.9)	13 (44.8)	131 (46.0)	
Left circumflex artery	37 (11.8)	5 (17.2)	32 (11.2)	
Strategy of PCI to culprit vessel				0.048
Implantation of drug-eluting stent	257 (81.8)	21 (72.4)	236 (82.8)	
Implantation of bare-metal stent	32 (10.2)	2 (6.9)	30 (10.5)	
Balloon angioplasty	24 (7.6)	6 (20.7)	18 (6.3)	
Catheter aspiration	1 (0.3)	0 (0)	1 (0.4)	
Peak serum creatine kinase, IU/l	1238 (390–3092)	604 (139–1921)	1337 (437–3197)	0.012
Systolic blood pressure, mmHg	116 (104–127)	115 (106–127)	116 (104–128)	0.873
Diastolic blood pressure, mmHg	68.5 ± 11.6	65.7 ± 10.7	68.8 ± 11.6	0.172
Left ventricular ejection fraction, %	56.9 ± 9.7	53.8 ± 11.4	57.3 ± 9.4	0.066
Hemoglobin, g/dl	12.4 ± 1.8	11.4 ± 1.7	12.5 ± 1.8	0.003
Serum creatinine, mg/dl	0.94 (0.81–1.11)	0.94 (0.81–1.41)	0.94 (0.81–1.10)	0.392
eGFR, ml/min/1.73 m <sup>2</sup>	60.0 (49.0–70.0)	50.7 (40.0–73.1)	60.0 (50.0–69.8)	0.136
Serum triglycerides, mg/dl	116 (92–149)	98 (78–144)	116 (95–151)	0.046
Serum LDL-cholesterol, mg/dl	95 (80–115)	87 (72–102)	96 (80–115)	0.025
Serum HDL-cholesterol, mg/dl	37 (31–46)	39 (34–48)	37 (30–46)	0.212
Blood glycosylated hemoglobin, %	5.8 (5.5–6.5)	5.8 (5.5–6.6)	5.8 (5.5–6.5)	0.565
Serum B-type natriuretic peptide, pg/ml	91 (35–213)	105 (61–505)	88 (33–206)	0.067
Medications at discharge				
Acetylsalicylic acid, <i>n</i> (%)	312 (99.4)	28 (96.6)	284 (99.6)	0.046
Clopidogrel, <i>n</i> (%)	303 (96.5)	27 (93.1)	276 (96.8)	0.297
Other P2Y <sub>12</sub> receptor inhibitors, <i>n</i> (%)	0 (0)	0 (0)	0 (0)	NA
Dual anti-platelet therapy (%)	301 (95.9)	26 (89.7)	275 (96.5)	0.078
Oral anticoagulant, <i>n</i> (%)	23 (7.3)	4 (13.8)	19 (6.7)	0.161
Statin, <i>n</i> (%)	292 (93.0)	28 (96.6)	264 (92.6)	0.431
ACE-I or ARB, <i>n</i> (%)	178 (55.4)	17 (58.6)	157 (55.1)	0.715
Beta-blocker, <i>n</i> (%)	169 (53.8)	14 (48.3)	155 (54.4)	0.530
Calcium channel blocker, <i>n</i> (%)	74 (23.6)	5 (17.2)	69 (24.2)	0.400
Nitrates (%)	7 (2.2)	2 (6.9)	5 (1.8)	0.074

**Table 1** (continued)

Variables	All subjects ( $n=314$ )	Patients with CVEs ( $n=29$ )	Patients without CVEs ( $n=285$ )	$P$ value
Diuretics, $n$ (%)	58 (18.5)	8 (27.6)	50 (17.5)	0.184
Oral glucose-lowering agents, $n$ (%)	74 (23.6)	9 (31.0)	65 (22.8)	0.325
Insulin, $n$ (%)	9 (2.9)	1 (3.4)	8 (2.8)	0.844

Data are expressed as number (percentages) of patients, mean  $\pm$  standard deviation for normal distribution, or median (interquartile ranges) for skewed distribution

*ACE-I* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CVEs* cardiovascular events, *eGFR* estimated glomerular filtration rate, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *NA* not applicable, *NSTEMI* non-ST-segment elevation myocardial infarction, *PCI* percutaneous coronary intervention, *STEMI* ST-segment elevation myocardial infarction

**Table 2** Clinical events recorded during the follow-up period

Clinical events	All subjects ( $n=314$ )	Patients with high ACI ( $n=125$ )	Patients with low ACI ( $n=189$ )	$P$ value
Follow-up period (months)	19.1 (12.8–25.8)	18.4 (11.9–25.0)	20.1 (13.1–26.0)	<0.001
Recurrent acute coronary syndrome, $n$ (%)	10 (3.2)	6 (4.8)	4 (2.1)	0.185
Stroke, $n$ (%)	14 (4.5)	11 (8.8)	3 (1.6)	0.002
Cardiovascular death, $n$ (%)	9 (2.9)	9 (7.2)	0 (0)	<0.001
Cardiovascular events, $n$ (%)	29 (9.2)	22 (17.6)	7 (3.7)	<0.001

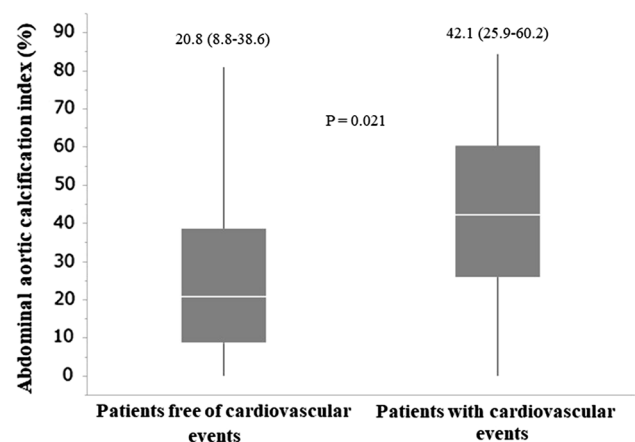
Data are number (percentages) of patients or median (interquartile ranges). High ACI was defined as  $ACI \geq 29.2\%$ ; low ACI was defined as  $ACI < 29.2\%$ . Cardiovascular events were defined as composite of cardiovascular death, recurrent acute coronary syndrome, and stroke

*ACI* abdominal aortic calcification index

cardiovascular-related (sudden cardiac death,  $n=4$ ; heart failure,  $n=3$ ; stroke,  $n=2$ ). Thus, the rate of CVEs was 9.2% (29 patients) in our cohort. In patients with CVEs, age and the prevalence of previous heart failure and left main coronary artery lesion were significantly higher, whereas body mass index, hemoglobin, and serum concentrations of peak creatine kinase, triglycerides and LDL-cholesterol were lower, compared to patients without (Table 1). Classification of ACS, culprit artery of ACS, and strategy of PCI to culprit vessel were also significantly different between patients with and without CVEs. In patients with CVEs, fewer were treated with acetylsalicylic acid, compared to those without CVEs.

ACI was 22.3 (9.4–42.1) % for the entire group. After adjustment for age and gender, multivariable regression analysis showed that ACI was significantly higher in patients with CVEs, compared to those without [42.1 (25.9–60.2) vs. 20.8 (8.8–38.6) %;  $P=0.021$ , Fig. 2]. Receiver-operating characteristic curve analysis showed a cutoff value of ACI of 29.2% for the prediction of CVEs, with sensitivity of 76% and specificity of 64% [area under the curve 0.69; 95% confidence interval (95% CI) 0.57–0.78] (Supplemental Fig. 2).

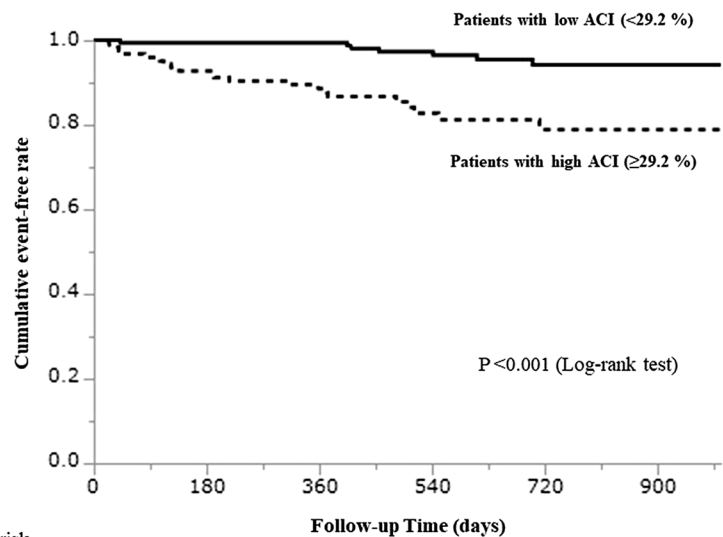
The rate of CVEs was significantly higher in patients with high ACI ( $\geq 29.2\%$ ) than in those with low ACI ( $< 29.2\%$ ) (Table 2). The rates of stroke and cardiovascular deaths were also significantly higher in patients with high ACI.



**Fig. 2** Comparison of abdominal aortic calcification index (%) of patients with and without cardiovascular events. Data were expressed as median (interquartile ranges) and analyzed by multivariable regression analysis after adjustment for age and gender. Cardiovascular events were defined as composite of cardiovascular death, recurrent acute coronary syndrome, and stroke

Kaplan–Meier analysis showed significantly worse event-free survival rate in patients with high ACI, compared to those with low ACI (log-rank test,  $P < 0.001$ ) (Fig. 3). Cox analysis adjusted for conventional cardiovascular risk factors showed that high ACI was significantly associated

**Fig. 3** Kaplan–Meier event-free survival curve for cardiovascular events. The event-free survival rate was significantly worse in patients with high ACI ( $\geq 29.2\%$ ; broken line) than in low ACI ( $< 29.2\%$ ; solid line) (log-rank test,  $P < 0.001$ ). Cardiovascular events were defined as composite of cardiovascular death, recurrent acute coronary syndrome, and stroke. ACI abdominal aortic calcification index



	Follow-up Time (days)					
Number of patients at risk	0	180	360	540	720	900
Patients with low ACI	189	187	166	117	74	27
Patients with high ACI	125	116	97	57	32	12

with CVEs [ $P = 0.011$ ; hazard ratio (HR) 1.82 (95% CI 1.15–3.02)], stroke [ $P = 0.024$ ; HR 2.21 (95% CI 1.11–5.02)] and cardiovascular death [ $P = 0.008$ ; HR  $4.13 \times 10^3$  (95% CI 1.55–not applicable)], but not with ACS recurrence [ $P = 0.477$ ; HR 1.37 (95% CI 0.61–3.20)]. In univariate Cox analysis, CVEs were significantly associated with high ACI, age, body mass index, history of heart failure, left main

coronary artery lesion, hemoglobin, serum concentrations of LDL-cholesterol, triglycerides, and BNP, and classification of ACS (Table 3). The risk of CVEs was significantly higher in NSTEMI, compared to STEMI [ $P = 0.015$ ; HR 2.83 (95% CI 1.24–6.34)]. It was lower in patients who had received drug-eluting stents [ $P = 0.005$ ; HR 0.27 (95% CI 0.11–0.68)] and bare-metal stents [ $P = 0.028$ ; HR 0.16 (95%

**Table 3** Cox analysis for the prediction of cardiovascular events

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> value
ACI $\geq 29.2\%$	2.20	1.50–3.40	$< 0.001$	1.80	1.14–2.96	0.012
Age (per 1 year increase)	1.05	1.02–1.09	0.001			
Body mass index (per 1.0 kg/m <sup>2</sup> increase)	0.87	0.78–0.97	0.010			
Previous heart failure	1.75	1.13–2.57	0.014			
Left main coronary artery lesion	2.02	1.17–3.15	0.015			
Hemoglobin (per 1.0 g/dl increase)	0.70	0.57–0.86	0.001			
Serum LDL-cholesterol (per 10 ml/dl increase)	0.86	0.74–1.00	0.042			
Serum triglycerides (per 10 ml/dl increase)	0.91	0.83–1.00	0.038			
Serum B-type natriuretic peptide (per 10 pg/ml increase)	1.02	1.01–1.02	0.005			
Hypertension	1.48	0.95–2.54	0.087			
Diabetes	1.19	0.81–1.70	0.369			
Dyslipidemia	0.84	0.58–1.21	0.333			
Acetylsalicylic acid at discharge	0.37	0.17–1.56	0.135			
eGFR (per 10 ml/min/1.73 m <sup>2</sup> increase)	0.83	0.68–1.01	0.068			
Left ventricular ejection fraction (per 10% increase)	0.76	0.52–1.12	0.163			
Classification of acute coronary syndrome			0.049 (for trend)			
Strategy of PCI to culprit vessel			0.065 (for trend)			

Multivariate model includes all variables at baseline with  $P < 0.05$  by univariate analysis

ACI abdominal aortic calcification index, CI confidence interval, eGFR estimated glomerular filtration rate, HR hazard ratio, LDL low-density lipoprotein, PCI percutaneous coronary intervention

CI 0.03–0.81)], compared to those treated by balloon angioplasty. Multivariate analysis identified high ACI as an independent and significant predictor of CVEs. Stepwise forward selection analysis identified high ACI ( $P=0.004$ ;  $R^2$ , 0.089) and history of heart failure ( $P=0.044$ ;  $R^2$ , 0.024) as independent determinants of CVEs. In addition, we evaluated whether the addition of ACI into the base model, together with conventional risk factors, improved the accuracy of prediction of CVEs. The addition of high ACI to conventional risk factors significantly improved both the net reclassification improvement (0.64;  $P=0.001$ ) and integrated discrimination improvement (0.04;  $P<0.001$ ), but not the C-index [ $P=0.279$ ; base model, 0.73 (95% CI 0.62–0.82) vs. model with high ACI, 0.76 (0.63–0.85)].

Finally, we examined the relationships between ACI and clinical characteristics by linear regression analysis. ACI was significantly associated with age ( $P<0.001$ ;  $\beta=1.12$ ), male sex ( $P<0.001$ ;  $\beta=-6.35$ ), body mass index ( $P<0.001$ ;  $\beta=-1.34$ ), hypertension ( $P<0.001$ ;  $\beta=5.29$ ), current smoking ( $P<0.001$ ;  $\beta=-5.01$ ), atrial fibrillation ( $P=0.016$ ;  $\beta=6.04$ ), history of MI ( $P=0.002$ ;  $\beta=5.55$ ), heart failure ( $P=0.001$ ;  $\beta=6.75$ ), systolic blood pressure ( $P=0.023$ ;  $\beta=0.19$ ), diastolic blood pressure ( $P<0.001$ ;  $\beta=-0.47$ ), hemoglobin ( $P<0.001$ ;  $\beta=-4.92$ ), LDL-cholesterol ( $P=0.008$ ;  $\beta=-0.12$ ), HDL-cholesterol ( $P=0.005$ ;  $\beta=0.33$ ), BNP ( $P<0.001$ ;  $\beta=0.03$ ), eGFR ( $P<0.001$ ;  $\beta=-0.29$ ), and LVEF ( $P=0.005$ ;  $\beta=-0.38$ ). Cox analysis adjusted for all these variables related to ACI ( $P<0.05$ ) demonstrated that high ACI was significantly associated with increased risk of CVEs [ $P=0.010$ ; HR 1.84 (95% CI 1.15–3.06)].

## Discussion

The present study investigated the association of ACI with mid-term CVEs in patients with ACS who had undergone PCI. Our observational study demonstrated that patients who developed CVEs had significantly higher ACI compared with those who did not. Furthermore, high ACI was an independent and significant predictor of mid-term CVEs, and was associated with stroke and cardiovascular death. In addition, the inclusion of ACI in the prediction model for CVEs improved the accuracy of the model. Previous studies reported the relationship between AAC and CVEs in several populations [6–10, 19, 20]. Furthermore, a meta-analysis of observational studies emphasized the predictive value of AAC for long-term CVEs [6], although the majority of the populations in these studies were individuals from the general population [7, 8]. The same relationship between AAC and CVEs was also reported in patients at high risk, such as those with chronic kidney disease or peripheral artery disease [10, 19, 20]. However, the value of AAC in predicting

secondary CVEs in patients with coronary artery disease has not been determined precisely. To the best of our knowledge, the present study is the first report to provide the prognostic value of AAC in patients with ACS.

Vascular calcification is an active and complex process involving numerous events leading to calcium deposition in the arterial wall [21]. These mechanisms include: (1) high serum levels of calcium and phosphate; (2) induction of osteogenesis; (3) inadequate inhibition of the mineralization process; and (4) migration and differentiation of macrophages and vascular smooth muscle cells into osteoclast-like cells [21–24]. Furthermore, the potential of a genetic mechanism is suggested in the development of vascular calcification [25]. Regardless of the exact mechanism, vascular calcification involves the formation of calcified deposits of hydroxyapatite crystals in the vascular wall. Vascular calcification is classified histopathologically into two categories: intimal and medial calcification [21]. Intimal calcification is associated with atherosclerotic plaques, whereas medial calcification is more widespread in the lower abdominal regions [22]. However, the underlying mechanisms of the relationship between AAC and CVEs have not been fully elucidated. Vascular calcification is associated with certain conventional cardiovascular risk factors [26]. ACI was also related to the same factors. Each segment of the vascular tree (e.g., abdominal aorta, coronary artery, and carotid-cerebral artery) is exposed to the same risk factors of atherosclerosis, and these risk factors can play important roles in the development of atherosclerosis at each segment. Thus, the relationship between AAC and CVEs is potentially influenced by the effects of conventional cardiovascular risk factors on coronary and carotid-cerebral artery, although high ACI was significantly associated with CVEs even after adjustment for those risk factors. In this regard, AAC is significantly associated with both coronary [13] and carotid artery calcification [27]. Patients with severe AAC may have more advanced atherosclerotic lesions in both coronary and carotid-cerebral arteries, resulting in increased risk of CVEs. Hence, AAC may be a surrogate marker of generalized systemic atherosclerosis, including the effects of conventional cardiovascular risk factors. Another explanation is that decreased vascular compliance associated with advanced AAC can lead to increased left ventricle afterload, resulting in left ventricular hypertrophy and heart failure [28, 29]. Decreased vascular compliance is also associated with increased pulse pressure [30], and the latter is reported to be an independent predictor of CVEs [31].

A meta-analysis of several observational studies concluded that AAC correlated with increased risks for coronary events, cerebrovascular events, and all CVEs [6]. A study from the Multi-Ethnic Study of Atherosclerosis showed that both AAC and coronary artery calcification could predict coronary artery disease and CVEs in

individuals free of cardiovascular diseases, whereas AAC alone was associated with cardiovascular mortality in the same population [32]. In the present study, AAC was significantly associated with stroke and cardiovascular death, but not with ACS recurrence in patients with ACS. The impact of AAC on secondary coronary events might be relatively small in patients with ACS, although the statistical power of the present study might be insufficient to allow proper evaluation of coronary events due to the small population and short follow-up period. Further studies of larger population samples and long-term follow-up are required to evaluate the exact impact of ACI on secondary coronary artery events in patients with ACS.

Previous studies discussed the relationship between thoracic aortic calcification and CVEs [33–35]. However, there were certain differences in the results of these studies. In a general cohort from the Multi-Ethnic Study of Atherosclerosis, thoracic aortic calcification was associated with coronary artery events only in women, independent of coronary artery calcification [33]. In another study involving a sample from the general population, thoracic aortic calcification was also associated with coronary artery events and all-cause mortality, but these relationships diminished following adjustment for coronary artery calcification [34]. In a retrospective small study, Yang et al. [35] found a significant relationship between aortic arch calcification and CVEs in patients with ACS. The prognostic value of thoracic aortic calcification for CVEs remains to be elucidated.

Although the present study identified the prognostic value of AAC in patients with ACS, abdominal CT scan is not a standard imaging procedure for patients with ACS in routine clinical practice. CT scan can potentially detect asymptomatic subclinical disorders. Previous studies indicated that the prevalence of abdominal aortic aneurysm was 2.4 times higher in patients with coronary heart disease than in the general population [36], whereas the incidence of cancer was higher in patients after MI [37]. However, radiation exposure and medical cost should be considered in CT scan. Accurate assessment of risk may be more important in high-risk patients. In this regard, our observations encourage assessment of AAC by abdominal CT scan, especially for patients with ACS and the following features: old age, low body mass index, heart failure, hypo-LDL-cholesterolemia, hyper-triglyceridemia, anemia, and left main coronary artery lesion.

At present, there are no established guidelines for secondary prevention in patients with severe AAC. Several studies showed some protective effects of bisphosphonates against the development of aortic and coronary artery calcification in patients on hemodialysis [38, 39]. However, a recent meta-analysis did not support any clinically important effects of bisphosphonates for cardiovascular events [40]. Given that conventional risk factors affect the development

of secondary CVEs in patients with severe AAC, a more aggressive approach towards these risks might be attributable to secondary prevention in patients with severe AAC. Further studies are needed to determine better management protocol for secondary prevention of CVEs in patients with severe AAC.

Lateral lumbar radiography is the traditional tool used to estimate the severity of AAC [6–9], whereas CT-based scoring methods have been adopted in recent studies [10, 13, 32, 41, 42]. Although the Agatston method was developed originally to evaluate coronary artery calcification [43], it has been also used to assess AAC in several studies [32, 41, 42]. Agatston score is calculated by multiplying each area of interest by a weighted score assigned to the highest density calcification within an individual area [43]. The AAC score derived by the Agatston method was reported not only to be associated with coronary artery disease [41], but also to predict CVEs in individuals free of cardiovascular diseases [32]. While the complexity of this method allows detailed calcification scoring, it often requires software to calculate the score. In the present study, we adopted the ACI, a semi-quantitative measure of AAC, in part due to the simplicity of this method. This score is calculated based on manual counting by physicians without the need for any expensive software. Although this scoring method has the potential to be observer-dependent, the inter- and intra-observer variabilities of ACI correlated well in the present study. Our results showed the prognostic value of ACI on mid-term CVEs in patients with ACS, whereas our previous study demonstrated the predictive value of ACI on long-term CVEs in patients with chronic kidney disease [10]. Another study reported that ACI was also significantly associated with severe coronary artery calcification in patients with chronic kidney disease who were free of coronary artery disease [13]. These findings highlight the importance of ACI as a useful tool for estimation of AAC in various clinical populations.

The present study has several limitations. First, this observational study was conducted in a single center and included a small population sample. Second, evaluation using multi-slice CT did not allow distinction between intimal and medial vascular calcification. Third, we did not compare ACI, a semi-quantitative tool based on non-contrast CT scan, with other quantitative methods by plain X-ray or CT scan. Fourth, radiation exposure should be considered in non-contrast CT scan, although CT scan is more sensitive in detecting vascular calcification than plain X-ray. Fifth, PCI strategy or additional medical therapies might influence mid-term CVEs. The risk of CVEs was significantly higher in patients treated by balloon angioplasty.

In conclusion, ACI was significantly associated with mid-term CVEs in patients with ACS after PCI. The addition of ACI to a model that included traditional risk factors improved the accuracy of prediction of CVEs.



Semi-quantitative evaluation of ACC using non-contrast CT scan seems to add valuable information and provide accurate assessment of mid-term CVEs in patients with ACS after PCI.

## Compliance with ethical standards

**Conflict of interest** All the authors declare no conflict of interest.

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