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Aortic arch calcification on chest X-ray combined with coronary calcium score show additional benefit for diagnosis and outcome in patients with angina

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Abstract

Background The coronary artery calcium (CAC) and aortic arch calcification (AoAC) are individually associated with cardiovascular disease and outcome. This study investigated the predictive value of AoAC combined with CAC for cardiovascular diagnosis and outcome in patients with angina. **Methods** A total of 2018 stable angina patients who underwent chest X-ray and cardiac multi-detector computed tomography were followed up for four years to assess adverse events, which were categorized as cardiac death, stroke, myocardial infarction, or repeated revascularization. The extent of AoAC on chest X-ray was graded on a scale from 0 to 3. **Results** During the four years of follow-up, 620 patients were treated by coronary stenting and 153 (7%) adverse events occurred. A higher grade of AoAC was associated with a higher CAC score. Cox regression showed that the CAC score, but not AoAC, were associated with adverse events. In patients with CAC score < 400, AoAC showed an additive predictive value in detecting significant coronary artery disease (CAD). A gradual increases in the risk of adverse events were noted if AoAC was present in patients with similar CAC score. **Conclusions** As AoAC is strongly correlated with the CAC score regardless of age or gender, careful evaluation of CAD would be required in patients with AoAC on conventional chest X-rays.

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Keywords: Aortic arch; Atherosclerosis; Calcification; Coronary artery disease

1 Introduction

Atherosclerosis is a diffuse progressive disorder and the major cause of cardiovascular disease. Vascular calcification occurs as atherosclerosis advances and can be quantified readily using non-invasive radiographic imaging techniques. Abundant evidence has reproducibly shown that high levels of coronary artery calcium (CAC) are correlated with clinically significant coronary artery disease (CAD) and can identify patients at risk for adverse cardiac events.[1–4] However, routine CAC screening has not been recommended because of radiation hazards, cost and insufficient evidence.[5,6] As vascular calcification would reflect overall systemic atherosclerotic burden, the association between coronary and extra-coronary calcification such as thoracic or abdominal aorta has been evaluated.[7–11] The results from these studies were obtained from lateral lumbar X-ray or CT procedures, which are not suitable for repeated assessments in clinical practice. Chest X-ray is a rapid screening tool that identifies the causes of chest pain or associated complications. Previous epidemiologic studies identified that aortic arch calcification (AoAC) detected on chest X-ray was associated with increased cardiovascular morbidity and mortality,[12–15] and AoAC was a strong independent predictor of cardiovascular events beyond traditional risk factors, including endothelial dysfunction.[12–15] These studies have some limitations that were small number in size and short-term follow-up in period. And then, it is not known whether AoAC correlates closely with the CAC score or whether AoAC could be additional benefit to predict adverse cardiac events compared with CAC score only. This study investigated the predictive value of AoAC combined with CAC for cardiovascular diagnosis and outcome in patients with angina.

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2 Methods

2.1 Study population

This was a single center cohort study of stable angina patients who underwent cardiac multi-detector computed tomography (MDCT) and chest X-ray within one month of each other from April 2008 to July 2009. The total number of cardiac MDCT examinations during this time span was 3454. Patients were excluded from the study if they had a prior diagnosis of acute myocardial infarction (AMI), catheterization-defined CAD, or prior revascularization therapy. The final study population consisted of 2018 patients, and they were retrospectively evaluated for the rates of significant CAD requiring coronary revascularization and occurrence of death from all causes, MI, repeated coronary revascularizations, or stroke over a mean follow-up period of 3.8 ± 0.7 years (range 0.7–5.1 years).

The study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of the Kyung Hee University College of Medicine (KMC IRB 1119-03). The committee waived the need for written informed consent from the participants.

2.2 Assessment of aortic arch calcification

Two independent observers (observer A, 5 years of experience; observer B, 11 years of experience) blindly reviewed the postero-anterior chest X-rays of all subjects. Conflicts were resolved by discussion with the senior author. The extent of AoAC in each chest X-ray assessed is shown in Figure 1. The AoAC was graded semi-quantitatively on a 4-point scale using a modified method based on previous reports: grade 0, no visible calcification; grade 1, < 50% calcification in the arch; grade 2, > 50% calcification; grade 3, circumferential calcification.[14,15] The concordance rate of this technique for grading was 94% in grade 0, 78% in grade 1, 74% in grade 2, and 96% in grade 3. Because grade 1 and 2 showed relatively low reproducibility, we categorized AoAC into three groups: grade 0, grade 1/2, and grade 3.

2.3 Assessment of coronary artery calcium score

CAC scoring was performed following the analysis of 64-slice cardiac MDCT scans (Brilliance 64, Philips Medical Systems, Best, the Netherlands) equipped with a standard cardiac reconstruction and post-processing package. Following scout chest radiography, a CAC score scan was performed using a 2.5-mm slice thickness, tube voltage of 120 kV, and tube current of 150 mA. Quantification of coronary calcification was performed using a dedicated 3D workstation (Extended Brilliance Workspace, Philips Medical Systems, Best, the Netherlands) by an experienced radiologist who was blinded to the clinical data of the participants. All pixels with a density > 130 Hounsfield units were automatically color marked, and the lesion was selected manually, followed by software recognition of the lesions on subsequent images. From the selected areas, the software calculated the lesion volume in cubic millimeters and the CAC score for each patient according to the Agatston method.[16] For further analysis, a CAC score was categorized into the either three groups (0–99, 100–399, ≥ 400) or two groups (< 100 and > 100).[17,18]

2.4 Clinical outcomes and study end points

The standard clinic examination included a physician-performed interview and physical examination. Age was assessed at the time of the cardiac MDCT scan in 2008–2009 and cardiovascular risk factor data assessed during a clinical visit within the same time frame. Coronary angiography (CAG) and percutaneous coronary intervention

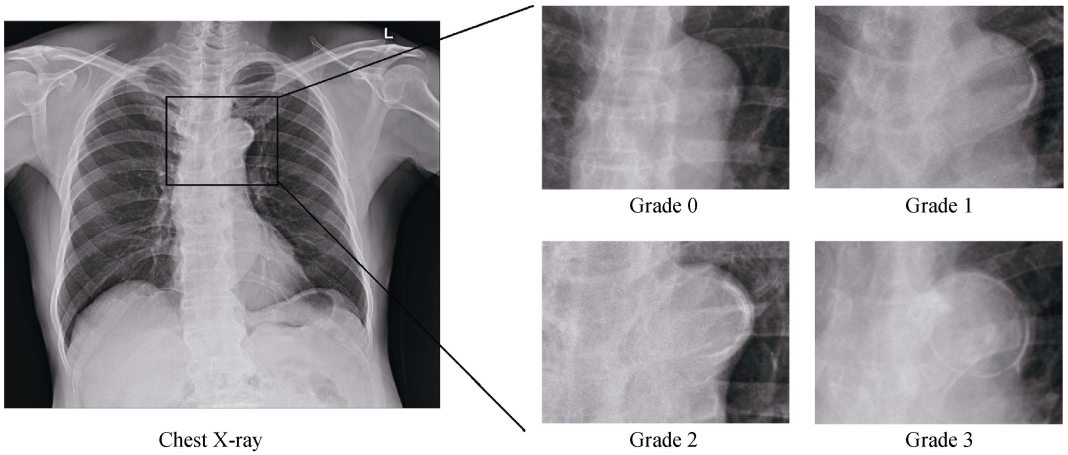


Figure 1. Assessment of aortic arch calcification from chest X-rays.

(PCI), if indicated, were performed using standard techniques. All procedural and technical details and the choice of devices were left to the physician's judgment. Clinical follow-up was performed via an office visit or telephone contact by researchers blinded to cardiac MDCT and clinical data. Hospital records were screened for clinical events to confirm the obtained information. The primary end points were the predictive values of long-term adverse outcomes, including death from all causes, MI, stroke, unplanned coronary revascularizations (> 90 days after MDCT scan) and repeated PCI after index PCI. The secondary end point included the correlation between AoAC and CAC scores.

2.5 Statistical analysis

The analyses were performed using SPSS version 17.0 (SPSS, Chicago, IL, USA). Differences were considered significant if the two-sided *P* value < 0.05. Continuous variables, presented as means ± SD, were evaluated for normal distribution and compared using analysis of variance. The continuous parameters with a skewed distribution were logarithmically transformed. Categorical variables, presented as frequencies and percentages, were compared using the Chi-square test or Fisher's exact test when appropriate. Correlations between two continuous variables were performed using the Pearson correlation coefficient or, if not normally distributed, the Spearman's rank correlation. Kaplan-Meier methods were used to describe survival curves according to AoAC and the CAC score. A multivariable logistic regression and cox proportional hazards model were used to estimate significant CAD and long-term clinical outcomes by model 1 (AoAC and CAC scores) and 2 (age, gender, diabetes, hypertension, smoking, dyslipidemia, chronic kidney disease, AoAC and CAC scores).

3 Results

The AoAC grades of the participants were distributed as follows: grade 0 (*n* = 1496, 74%), grade 1 (*n* = 256, 13%), grade 2 (*n* = 178, 9%) and grade 3 (*n* = 88, 4%). The mean CAC score was 143 (range: 0–7895). Baseline characteristics, cardiovascular risk factors, concomitant medications and laboratory findings of the study population according to the AoAC grades are summarized in Table 1. There were positive associations between AoAC grade and the following variables: age, systolic blood pressure, body mass index, high-sensitivity C-reactive protein, N-terminal pro-brain natriuretic peptide, hemoglobin A1c, current smoking, prevalence of diabetes, hypertension, and chronic kidney disease, as well as previous history of stroke and heart failure. The AoAC grade was negatively correlated with high-density lipoprotein cholesterol but not with other lipid parameters. A previous history of angina was not significantly associated with the AoAC grade.

Table 1. Demographics according to aortic arch calcification.

	Grade 0 (*n* = 1496)	Grade 1/2 (*n* = 434)	Grade 3 (*n* = 88)	*P* value
Age, yrs	58.9 ± 10.9	68.6 ± 8.7	72.2 ± 7.9	< 0.001
Male gender	798 (53%)	184 (42%)	22 (25%)	< 0.001
Framingham risk score	12.6 ± 4.8	16.0 ± 3.6	17.6 ± 3.2	< 0.001
Hypertension	843 (57%)	333 (78%)	71 (81%)	< 0.001
Diabetes mellitus	377 (26%)	149 (35%)	30 (34%)	< 0.001
Dyslipidemia	538 (51%)	182 (60%)	36 (54%)	0.02
Current smoker	343 (32%)	110 (31%)	11 (14%)	0.004
Previous stroke	153 (10%)	72 (17%)	13 (15%)	0.001
Chronic kidney disease	77 (5%)	60 (14%)	27 (31%)	< 0.001
History of heart failure	47 (3%)	31 (7%)	8 (9%)	< 0.001
Any antiplatelet agents	648 (43%)	250 (58%)	50 (57%)	< 0.001
β-blocker	340 (23%)	136 (32%)	35 (40%)	< 0.001
ACE inhibitor or ARB	451 (30%)	192 (44%)	43 (49%)	< 0.001
Calcium channel blocker	417 (28%)	170 (39%)	32 (36%)	< 0.001
Statins	451 (30%)	152 (35%)	32 (36%)	0.09
Creatinine, mg/dL	0.9 ± 0.9	1.1 ± 1.6	1.3 ± 1.7	< 0.001
Total cholesterol, mg/dL	180.6 ± 42.6	177.2 ± 41.7	179.6 ± 48.4	0.37
Triglyceride, mg/dL	141.5 ± 76.9	138.0 ± 72.1	140.4 ± 71.9	0.71
HDL-cholesterol, mg/dL	50.1 ± 13.6	47.8 ± 13.0	45.2 ± 11.5	< 0.001
LDL-cholesterol, mg/dL	110.9 ± 36.0	108.1 ± 37.1	110.1 ± 36.4	0.44
Calcium, mg/dL	8.9 ± 0.6	8.8 ± 0.8	8.8 ± 0.5	0.60
Phosphate, mg/dL	3.5 ± 0.6	3.5 ± 0.8	3.7 ± 0.6	0.04
ALP, IU/L	68.6 ± 25.4	70.7 ± 30.3	75.2 ± 26.7	0.04
hsCRP, mg/L	0.8 (0.4–2.1)	1.0 (0.5 – 3.2)	0.9 (0.5 – 2.5)	0.003
NT-proBNP, pg/mL	54.6 (24.4 – 133.0)	113.5 (47.1 – 463.0)	295.0 (76.9 – 900.7)	< 0.001
HbA1c, %	6.3 ± 1.1	6.5 ± 1.3	6.4 ± 1.3	0.002

Data are presented as *n* (%), means ± SD or median (range) unless other indicated. ACE: angiotensin converting enzyme; ALP: alkaline phospatase; ARB: angiotensin receptor blocker; HbA1c: hemoglobin A1c; HDL: high density lipoprotein; hsCRP: high-sensitivity C-reactive protein; LDL: low density lipoprotein; NT-proBNP: N-terminal pro-brain natriuretic peptide.

As shown in Figure 2A and 2B, subjects with lower grades of AoAC had lower CAC scores, and a greater number had a CAC score of 0–99. Subjects with higher grades of AoAC had higher CAC scores, and a greater number had CAC scores > 400. Regardless of gender (Figure 2C) and age (Figure 2D) differences, AoAC grades were positively associated with the CAC score.

The results of clinical outcome are shown in Table 2. With increasing grades or scores of AoAC and CAC, there were significantly higher rates of CAD and total adverse events. In a regression model 1, AoAC and CAC score were independent predictors of significant CAD (Table 3), but the CAC score was an independent predictor of significant CAD adjusted by model 2 (age, gender, diabetes, hypertension, smoking, dyslipidemia, and chronic kidney disease). As shown in Table 3, the CAC score, but not AoAC, was an independent predictor of long-term adverse outcomes by model 1 and 2. Figure 3 shows the hazard ratio for total adverse events according to the CAC score with the presence or absence of AoAC using Kaplan-Meier analysis. If the CAC score cutoff value was set at 100, the presence of AoAC had a stepwise incremental predictive value for adverse events in patients with similar CAC scores.

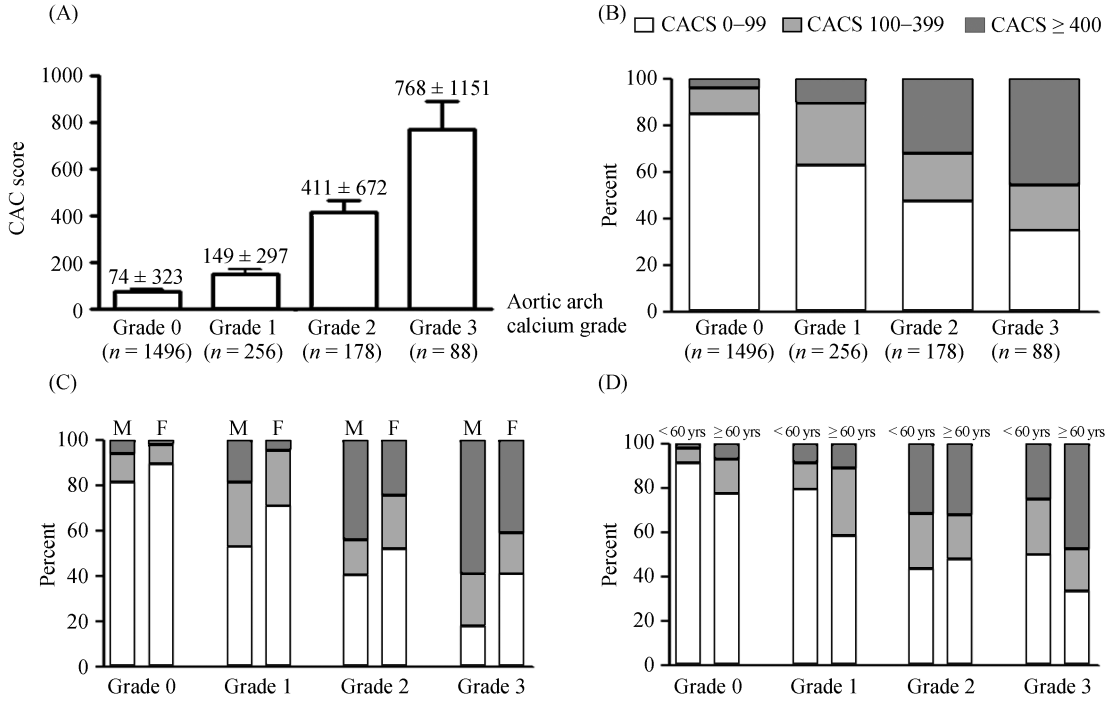


Figure 2. Correlation between AoAC and the CAC score. (A): Differences in the CAC score according to AoAC grades in all subjects; (B): distribution of the CAC score according to AoAC grades in all subjects; (C): distribution of the CAC score and AoAC grades according to gender; and (D) distribution of the CAC score and AoAC grades according to age (< 60 and ≥ 60 years). AoAC: aortic arch calcification; CAC: coronary artery calcium.

Table 2. The incidence of significant coronary artery disease and clinical outcomes.

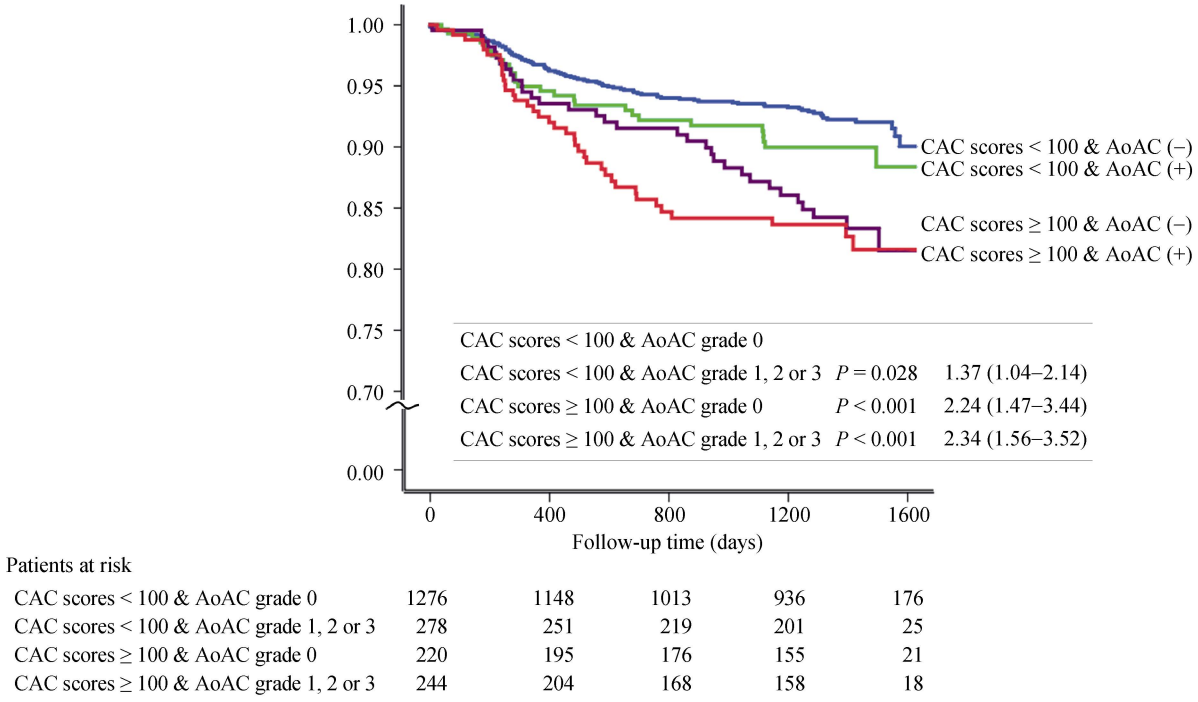
	Aortic arch calcification			*P* value	Coronary artery calcium score			*P* value
	Grade 0 (*n* = 1496)	Grade 1/2 (*n* = 434)	Grade 3 (*n* = 88)		0–99 (*n* = 1554)	100–399 (*n* = 278)	≥ 400 (*n* = 186)	
Significant CAD	388 (25.9%)	184 (42.4%)	48 (54.5%)	< 0.001	355 (22.3%)	144 (51.8%)	121 (65.1%)	< 0.001
Total adverse outcomes	126 (8.4%)	48 (11.1%)	17 (19.3%)	< 0.001	120 (7.7%)	35 (12.6%)	36 (19.4%)	< 0.001
Death	1 (0.1%)	1 (0.2%)	0	0.61	1 (0.1%)	0	1 (0.5%)	0.13
MI	6 (0.4%)	0	1 (1.1%)	0.94	4 (0.3%)	1 (0.4%)	2 (1.1%)	0.10
Unplanned PCI	61 (4.7%)	17 (3.9%)	5 (5.7%)	0.74	51 (3.3%)	15 (5.4%)	17 (9.1%)	< 0.001
Repeated PCI	28 (1.9%)	13 (3.0%)	4 (4.5%)	0.12	30 (1.9%)	6 (2.2%)	9 (4.8%)	0.04
CABG	1 (0.1%)	0	1 (1.1%)	0.07	0	0	2 (1.1%)	< 0.001
Stroke	29 (1.9%)	17 (3.9%)	6 (6.8%)	< 0.001	34 (2.2%)	13 (4.7%)	5 (2.6%)	0.05

Data are presented as *n* (%). CABG: coronary artery bypass graft surgery; CAD: coronary artery disease; CVD: cerebrovascular disease; MI: myocardial infarction; PCI: percutaneous coronary intervention.

Table 3. Univariate and multivariate Cox proportional hazards analysis.

	Prediction of significant CAD				Prediction of total adverse events			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	P value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)
Aortic arch calcification grade	< 0.001		0.006		0.001		0.26	
Grade 0	N/A	1	N/A	1	N/A	1	N/A	1
Grade 1/2	< 0.001	2.10 (1.68–2.63)	0.005	1.42 (1.11–1.81)	0.07	1.36 (0.98–1.89)	0.65	1.08 (0.76–1.54)
Grade 3	< 0.001	3.42 (2.22–5.29)	0.04	1.64 (1.01–2.67)	< 0.001	2.51 (1.51–4.17)	0.10	1.59 (0.91–2.77)
Coronary artery calcium score	< 0.001		< 0.001		< 0.001		< 0.001	
0–99	N/A	1	N/A	1	N/A	1	N/A	1
100–399	< 0.001	3.63 (2.79–4.72)	< 0.001	3.32 (2.54–4.35)	0.009	1.65 (1.13–2.41)	0.02	1.59 (1.08–2.34)
≥ 400	< 0.001	6.29 (4.55–8.69)	< 0.001	5.21 (3.69–7.35)	< 0.001	2.84 (1.96–4.12)	< 0.001	2.50 (1.65–3.79)

CAD: coronary artery disease; N/A: not assessable.



Patients at risk

CAC scores < 100 & AoAC grade 0	1276	1148	1013	936	176
CAC scores < 100 & AoAC grade 1, 2 or 3	278	251	219	201	25
CAC scores ≥ 100 & AoAC grade 0	220	195	176	155	21
CAC scores ≥ 100 & AoAC grade 1, 2 or 3	244	204	168	158	18

Figure 3. Kaplan-meier analysis. Total adverse events according to the CAC score with the presence or absence of AoAC. AoAC: aortic arch calcification; CAC: coronary artery calcium.

4 Discussion

The major findings of this cohort study were as follows: (1) AoAC evaluated on conventional chest X-rays strongly correlated with the CAC score on cardiac MDCT, regardless of age or gender; and (2) Although AoAC itself was not an independent predictor compared with CAC scores, AoAC evaluation could be valuable because the presence of AoAC had an additional benefit in subjects with similar CAC scores.

The correlation of calcifications in the coronary arteries and the aorta have been evaluated using several non-invasive imaging techniques, such as plain chest, abdomen, and lumbar X-rays, CT, electron beam CT (EBCT) and MDCT.[7–11] In addition, the prognostic implications of calcifications in the aortic arch, thoracic or abdominal aorta, alone or in combination, have been assessed for adverse cardiovascular events.[12,13,15,19–25] This leads to questions concerning the level of calcification in the aorta that would predict future cardiovascular events greater than would the

CAC score. While calcification of the thoracic aorta is associated with the CAC score, it was not shown to have a greater predictive value over CAC.[9,10] In the abdominal aorta, a significant correlation with future cardiovascular events was found in 2467 Framingham Heart Study participants using plain abdominal X-ray during a 22-year period.[21,22] There are no reports comparing the predictive value of AoAC or abdominal aorta calcification for cardiovascular events with that of the CAC score, although many studies have shown that AoAC or abdominal aorta calcification was positively associated with CAC scores and future cardiovascular events.[12–14,15,21,22] It is generally accepted that a plain chest X-ray is a diagnostic baseline procedure in patients with chest discomfort. This study, as well as others, has demonstrated that assessment of AoAC on a chest X-ray is a simple and reliable method for risk assessment.

In contrast to the atherosclerotic features of coronary calcium, aortic calcification can be divided into two separate pathophysiological processes: intimal, which is primarily atherosclerotic, and medial, which is not atherosclerotic.[12,23] Intimal calcification was associated with plaque vulnerability,[24] observed as a spotty and patchy radio-opaque finding. Medial calcification is usually associated with aging, end-stage renal disease and diabetes. It is seen as continuous linear deposits along the internal elastic lamina. However, it is difficult to distinguish these calcific changes in the arterial wall solely by radiographic techniques without using a pathologic approach. AoAC was correlated with carotid intima media thickness, pulse wave velocity, and poor flow mediated dilation,[15] suggesting that AoAC and CAC may have similar pathogeneses.

MDCT provides highly accurate information on coronary artery stenosis with excellent sensitivity and negative predictive value.[1–4] This commercially available scan also provides an accurate assessment of the amount of calcification for total or individual coronary arteries, and the result can be achieved quickly during a single breath-hold of a few seconds. Although CAC evaluation can provide additional information identifying patients at risk for adverse cardiac events,[1–4] it requires special equipment, is expensive to perform and is not suitable for repeated assessment in clinical practice. Additionally, routine CAC scanning of the asymptomatic adult population is not currently recommended, and there is little evidence determining the CAC score in an individual patient resulted in improved outcomes and reduced coronary events. Importantly, there are concerns regarding the associated radiation exposure.[25–27] Although the usual radiation dose for detecting CAC is relatively low (generally, 0.6–1.0 mSv for EBCT and 0.9–2.0 mSv for MDCT),[28] some MDCT imaging protocols are associated with estimated radiation doses > 10 mSv.[25] Einstein, *et al.*,[29] calculated that the risk for future cancer using MDCT at 14 mSv in a 20-year-old woman was estimated to be 1 in 219, compared with 1 in 715 in a 60-year-old woman and 1 in 1911 in a 60-year-old man (9 mSv). In comparison, chest X-rays are less expensive, easy to follow-up routinely and yield a radiation dose of 0.01–0.02 mSv.[26,27] As AoAC is strongly correlated with the CAC score regardless of age or gender, careful evaluation of CAD would be required in patients with AoAC on conventional chest X-rays. In the present study, we examined AoAC using a simple standard chest X-ray method to investigate the prognostic features of cardiovascular events. As shown in Figure 3, the presence of AoAC showed additive predictive role in patients with CAC score < 100. It suggests AoAC evaluation would be more valuable in low to intermediate-risk probability groups. These could be valuable findings, since the current American Heart Association and European Society of Cardiology guidelines mention that CAC testing is not suitable for low-risk patients.

The recent PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial was performed with the enthusiasm evaluating the critical coronary stenosis to improve the prognosis of CAD patients. But anatomical approach did not achieve the superiority in clinical outcomes than functional testing strategy although we need to concern its inconclusive result due to limited statistical power.[30] In clinical practice, we could experience some patients with signs and symptoms of myocardial ischemia have normal or insignificant degree of coronary stenosis, and vise versa, others with severe CAD have neither any chest pain nor evidence of myocardial ischemia.[31] These suggest identification of anatomically obstructive CAD is not solely diagnostic work-up, rather understanding of atherosclerosis and functional status would improve patients' prognosis. But this study did not include the associations of AoAC and the results of functional tests. Other limitations were as follows: this study evaluated non-randomized, observational registry data. As in any observational cohort study, residual confounding is of concern. Additionally, only a small number of high-risk patients (23 patients with CACS ≥ 400) were included, which necessitates further studies using a larger group of patients.

Despite these drawbacks, AoAC combined with the CAC score is a valuable tool. In patients with similar CAC scores, AoAC was associated with an increasing risk of adverse events, suggesting that careful attention should be given to the presence of AoAC on plain chest X-ray.

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