Coronary Calcium Score as a Predictor for Coronary Artery Disease and Cardiac Events in Japanese High-Risk Patients

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Background: Although the coronary artery calcium (CAC) score as measured with computed tomography (CT) is associated with cardiovascular mortality and morbidity in Western countries, little is known in Asian populations.

Methods and Results: Three hundred and seventeen Japanese patients (205 men and 112 women) were followed in the study and they underwent both coronary angiography and CT for CAC measurements. The frequencies of angiographic coronary artery disease (CAD) were 5%, 36%, 76%, 80%, and 94% (P<0.001) and the needs for revascularization were 5%, 26%, 53%, 59%, and 69% (P<0.001) in patients with CAC scores of 0 (n=64), 1–100 (n=58), 101–400 (n=76), 401–1,000 (n=70), and >1,000 (n=49), respectively. In the average of 6.0 (range, 1–10) years follow-up period, 34 patients died including 13 from reasons of cardiac disease. In a Cox proportional hazard model after adjustment for age and sex, traditional coronary risk factors, previous myocardial infarction, and the need for revascularization, the hazard ratio for cardiac mortality in patients with a CAC score >1,000 was 2.98 (95% confidence interval: 1.15–9.40) compared with those with a CAC score=0–100.

Conclusions: The CAC score has a predictive value for angiographical CAD and long-term mortality from cardiac disease in Japanese high-risk patients who undergo coronary angiography. (*Circ J* 2011; **75**: 2424–2431)

Key Words: Cardiovascular disease mortality; Coronary angiography; Coronary calcification

Coronary artery calcium (CAC) is considered to be a surrogate marker for the presence and amount of coronary subclinical atherosclerosis.[1–3] Many studies using electron-beam tomography or multidetector computed tomography (CT) have suggested that the presence and extent of CAC strongly correlates with the overall atherosclerotic plaque burden and with the development of subsequent coronary events in Western countries.[4–8] However, in Asians, the association between CAC scores and the prevalence of coronary artery disease (CAD) has not been fully evaluated, and it is also unclear whether CAC scores have a predictive value for cardiovascular events in CAD patients. The Multi-ethnic Study of Atherosclerosis (MESA) has demonstrated that the CAC score in Asians (mostly Chinese) is not significant for major coronary events.[6]

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Recent advances in technology of coronary CT angiography

(CTA) have enabled the detection of coronary artery stenosis non-invasively[9–13] and the identification and characterization of non-calcified plaques that might be prone to developing acute coronary syndrome.[14–16] However, it is unclear whether detection and characterization of non-calcified plaques are more predictive for future coronary events than measurement of CAC scores.

In the present study, we investigated whether the CAC score was associated with the presence of CAD and future cardiovascular events in Japanese high-risk patients who underwent invasive coronary angiography.

Methods

Subjects
Between 1993 and 2005, a total of 723 patients underwent cardiac CT for measurement of CAC scores, and 428 patients were referred for invasive coronary angiography. Performance of angiography was not conditional on the results of the CAC

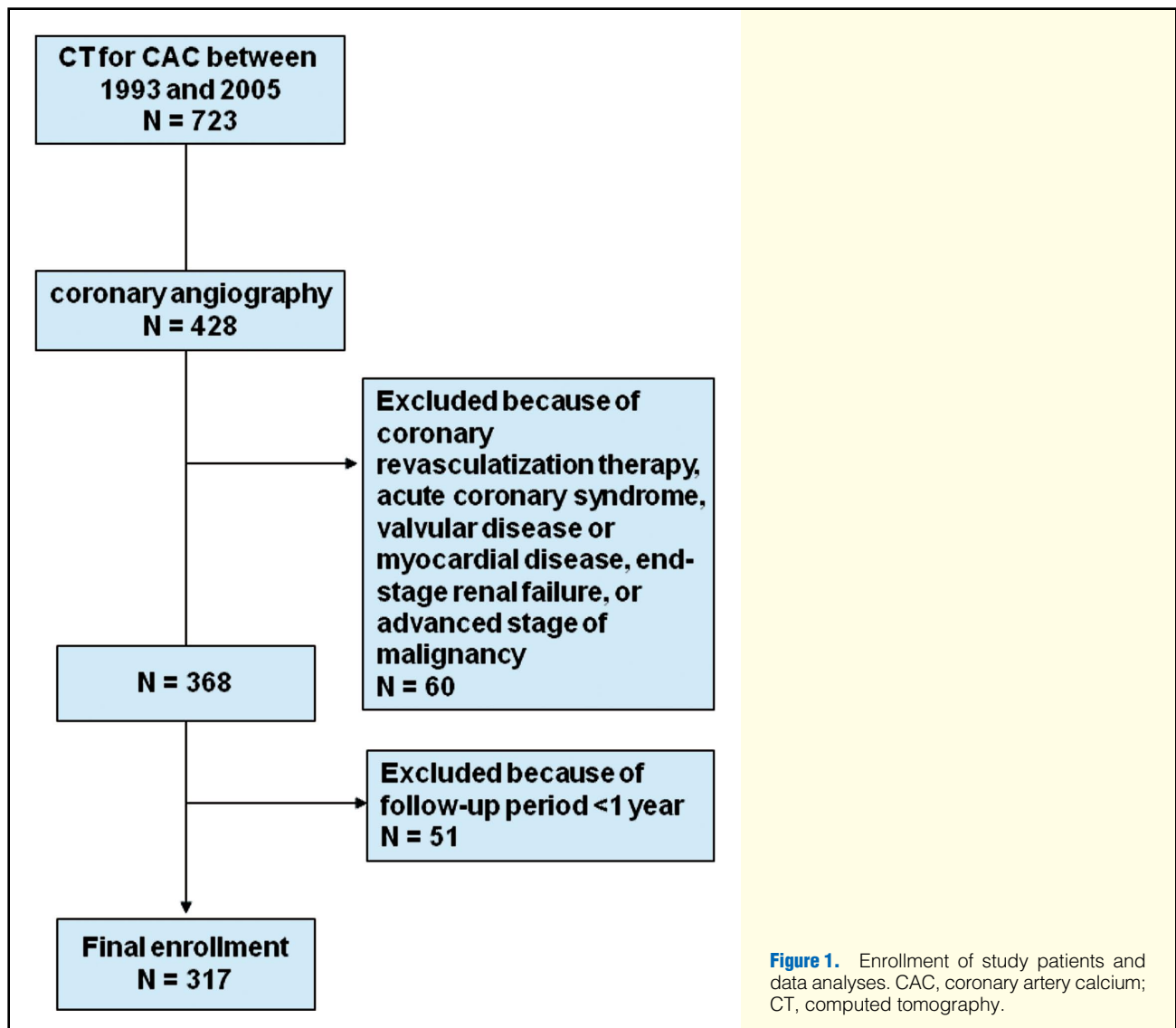**Figure 1.** Enrollment of study patients and data analyses. CAC, coronary artery calcium; CT, computed tomography.

score. We excluded patients with previous coronary revascularization therapy as follows: percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery, acute coronary syndrome, valvular disease or myocardial disease, end-stage renal failure, or an advanced stage of malignancy. Out of the remaining 368 patients, we excluded 51 patients who could not be followed-up over 1 year. Finally, we included 317 patients consisting of 205 men and 112 women (age, 65.8±10.4 years) to analyze the prevalence of angiographical CAD, the need for revascularization therapy after CT examination, and cardiovascular events (**Figure 1**). For the indication of coronary angiography, 82% of patients underwent coronary angiography for evaluation of chest pain, and the remaining 18% were asymptomatic, but they had ECG abnormalities or positive stress tests. The study was approved by the hospital's ethical committee.

Coronary Risk Factors
All patients provided details of their demographics and medical history at administration for coronary angiography. If subjects were current smokers, they were considered to have a positive history of cigarette smoking. Hypertension was

defined if systolic blood pressure was ≥140 mmHg, diastolic blood pressure was ≥90 mmHg, and/or under antihypertensive therapy. Diabetes mellitus was self-reported by patients and current use of hypoglycemic agents. Hypercholesterolemia was characterized by a fasting serum low-density lipoprotein cholesterol level ≥140 mg/dl from the Friedewald equation,[17] or when the patient was using lipid-lowering agents.

Coronary CT Scanning and CAC Measurements
A plain scan to measure the CAC score with prospective electrocardiographic gating was performed. We used electron-beam CT (Imatron C-150XL, GE-Imatron, South San Francisco, CA, USA) between 1993 and 2003, and 16-multi-detector CT (Lightspeed Ultra-16, GE Healthcare, Waukesha, WI, USA) between 2004 and 2005. In the scans using electron beam CT (130 kV and 625 mA), single-section mode images were obtained using electrocardiogram-triggered to 80% of the R-R interval for standardized calcium scoring with a 100-ms acquisition time. A 512×512 matrix with the smallest possible field-of-view was used. Thirty-five to 40 continuous gapless slices of 3-mm thickness were obtained starting 9 mm above the left main coronary artery to the bottom of both

Table 1. Patients' Characteristics Among CAC Score Classes

CAC score	All (n=317)	0 (n=64)	1–100 (n=58)	101–400 (n=76)	401–1,000 (n=70)	>1,000 (n=49)	P value
Age (years)	65.8±10.4	61.8±12.5	62.5±9.4	66.9±10.6	68.3±8.9	69.6±7.0	<0.001
Male (%)	61	53	60	76	59	74	0.018
Hypertension (%)	61	48	49	66	63	76	0.025
Hypercholesterolemia (%)	44	32	40	47	59	40	0.036
Diabetes mellitus (%)	46	25	40	53	47	66	<0.001
Cigarette smoking (%)	47	37	51	51	42	51	0.53
Previous MI (%)	14	2	10	14	25	20	0.0004
Angiographic CAD (%)	58	5	36	76	80	94	<0.001
1-vessel disease (%)	21	3	26	36	33	18	
2-vessel disease (%)	16	0	5	22	31	37	<0.001
3-vessel disease (%)	12	2	3	16	17	37	
Need for revascularization (%)	42	5	26	53	59	69	<0.001
PCI (%)	31	5	22	41	44	39	
CABG (%)	11	0	3	12	14	29	

Data are expressed as mean±SD or percent.
CAC, coronary artery calcium; MI, myocardial infarction; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

ventricles. In 16-multidetector CT with an axial scan, gantry rotation time was 500 ms, X-ray exposure time was 333 ms, tube voltage was 120 kV, tube current was 100 mA, and the center of the imaging window was 75% of R-R. Thirty-five to 40 contiguous images of 2.5-mm thickness were obtained.

A CAC score was calculated according to the Agatston method as previously described.[18] The Agatston calcium score was determined on commercially available external workstations. AccuImage (AccuImage Diagnostic Corporation, San Francisco, CA, USA) was used for data from the electron beam CT and Smartscore, version 4.2 (GE Healthcare), for data from the 16-slice CT.[19,20] According to a previous report, the correlation between 2 CT scanners was found to be high for calcium score (r^2=0.955) compared with CAC score quantification in 100 patients.[19]

Coronary Angiography and Revascularization

All patients underwent coronary angiography as clinically indicated for presumed angiographic CAD. Selective coronary angiography was performed by the Judkins technique. Observers who had no knowledge of the CT findings reviewed all coronary angiographies. Each coronary vessel (the left main, left anterior descending, left circumflex, and right coronary arteries) was assessed, and visual estimation of the percent luminal stenosis for each lesion was recorded. Angiographic CAD was defined if >50% luminal diameter stenosis was found in any vessel and the number of vessels with >50% stenosis was assessed. Coronary revascularization was considered if either PCI or CABG was decided according to the preceding results from coronary angiography <2 months after CT examination for CAC scoring.

Patient Follow-up and Cardiovascular Events

Patients were followed for a mean of 6.0±2.4 years (range, 1–10 years). The patients' information was obtained from the medical records, by telephone interview for patients or their family, or by questionnaires for their primary care physicians. All endpoints were determined by consensus of 2 reviewers blinded to the results of CT and angiography and previous hospitalizations. Patients with acute myocardial infarction (MI) had 2 of the 3 criteria: chest pain lasting over 30 min,

elevation of serum creatine kinase with a myocardial-bound fraction, and new pathological Q waves of 0.04 s duration. Cardiac death included death from MI and heart failure or sudden cardiac death. The primary endpoint for the study was mortality for all-cause and cardiac disease. Hard events included cardiac death and non-fatal MI.

Statistics

The CAC score was expressed as a median value (interquartile range). Other measurements were expressed as mean±SD. We used the Mann-Whitney test and analysis of variance, including Tukey's test for multiple comparisons, to compare continuous variables between the groups. Categorical variables were reported as number (%) and were compared using Pearson's chi-square test. A receiver operated characteristic (ROC) analysis was performed to determine the increase of CAC scores in prediction of future events. Univariable and multivariable Cox proportional hazard regression models were used to determine the predictor of future events. Clinical characteristics and angiographic results were compared among the 5 groups: CAC score=0, 1–100, 101–400, 401–1,000, and >1,000 according to previous studies.[4–6] Event rates were estimated by Kaplan–Meier curves and compared by log-rank test among the 3 groups: CAC score=0–100, 101–1,000, and >1,000. Unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CI) for all-cause and cardiac mortality, and hard events in patients with a CAC score >1,000 and CAC score of 101–1,000 were calculated with a CAC score of 0–100 as a reference. All statistical analyses were performed using JMP for Windows version 5.1 (SAS Institute, Cary, NC, USA). A P-value of <0.05 was considered statistically significant.

Results

Patients' Characteristics, Prevalence of Angiographic CAD, and Needs for Revascularization

Table 1 shows the clinical findings among 5 classes according to the CAC scores. Age and frequencies of male sex, diabetes mellitus, and previous MI were significantly increased across the CAC score categories.

Table 2. Event Numbers and Annual Rates According to CAC Categories

	All (n=317)	0 (n=64)	1–100 (n=58)	101–400 (n=76)	401–1,000 (n=70)	>1,000 (n=49)	P value
All-cause death (n)	34	7	3	5	9	10	
Annual rate (%)	1.78	1.70	0.76	1.17	2.17	3.71	<0.0001
Cardiac death (n)	13	1	1	2	1	8	
Annual rate (%)	0.68	0.24	0.26	0.46	0.14	2.84	<0.0001
Hard events (n)	24	1	4	8	2	9	
Annual rate (%)	1.30	0.24	1.05	1.93	0.29	3.19	<0.0001

Abbreviation see in Table 1.

Table 3. Unadjusted and Adjusted HR for Cardiac Death by the Cox-Proportional Model

	Unadjusted		Adjusted	
	HR (95%CI)	P value	HR (95%CI)	P value
Age (per 10 years)	0.912 (0.56–1.58)	0.74	0.98 (0.92–1.04)	0.55
Male	1.37 (0.75–2.88)	0.32	1.64 (0.70–4.54)	0.26
Hypertension	1.50 (0.82–3.18)	0.20	1.22 (0.64–2.65)	0.55
Hyperlipidemia	1.09 (0.62–1.90)	0.76	1.01 (0.55–1.86)	0.98
Diabetes mellitus	1.67 (0.95–3.22)	0.07	1.46 (0.76–3.19)	0.26
Cigarette smoking	1.12 (0.63–2.02)	0.68	0.99 (0.49–2.07)	0.98
Previous MI	1.24 (0.58–2.24)	0.54	1.13 (0.51–2.27)	0.72
Coronary revascularization	1.28 (0.74–2.26)	0.37	0.85 (0.44–1.67)	0.64
CAC score (per 100)	1.06 (1.03–1.09)	0.0005	1.06 (1.02–1.12)	0.006

HR, hazard ratio; CI, confidence interval. Other abbreviations see in Table 1.

Out of a total of 317 patients, 184 patients (58%) had angiographical CAD and 133 (42%) needed revascularization consisting of 98 (31%) PCI and 35 (11%) CABG. The prevalence of angiographic CAD was hierarchically increased across the CAC score classes (CAC score=0, 5%; 1–100, 36%; 101–400, 76%; 401–1,000, 80%; >1,000, 94%; P<0.001). The incidences of revascularization after CAC measurements were 5%, 26%, 53%, 59%, and 69% in patients with a CAC score of 0, 1–100, 101–400, 401–1,000, and >1,000, respectively (P<0.001). We found that angiographic CAD and the need for revascularization were both 5% in patients with CAC score=0: 2 patients had 1-vessel disease and 1 patient had 3-vessel disease.

Predictor for CV Events and Mortality

A total of 34 patients died; 13 were cardiac deaths and 21 were non-cardiac deaths. Hard events were observed in 24 patients consisting of 11 non-fatal MI. In patients with CAC=0, we found 1 sudden cardiac death and 5 non-cardiac cardiovascular deaths (2 with renal failure and 3 with cerebrovascular disease, and 1 cancer death) (**Table 2**). Using ROC analysis to compare the predictive power of the CAC scores, the area under the curve was 0.62, 0.73, and 0.62, in prediction of all-cause and cardiac mortality, and major cardiovascular events, respectively (**Figure 2**).

A Cox-proportional model showed that an increase in the CAC score was significantly related to cardiac mortality in a univariate model (unadjusted HR per 100 increase in CAC score, 1.06; 95%CI, 1.03–1.09; P=0.0005). A multivariable model showed that the CAC score was an independent predictor (adjusted HR per 100 increase in CAC score, 1.06; 95%CI, 1.02–1.12; P=0.006) (**Table 3**).

Kaplan–Meier survival curves were free from all-cause death, cardiac death, and hard events according to the 3 classes of CAC scores. Patients with a CAC score >1,000 had the
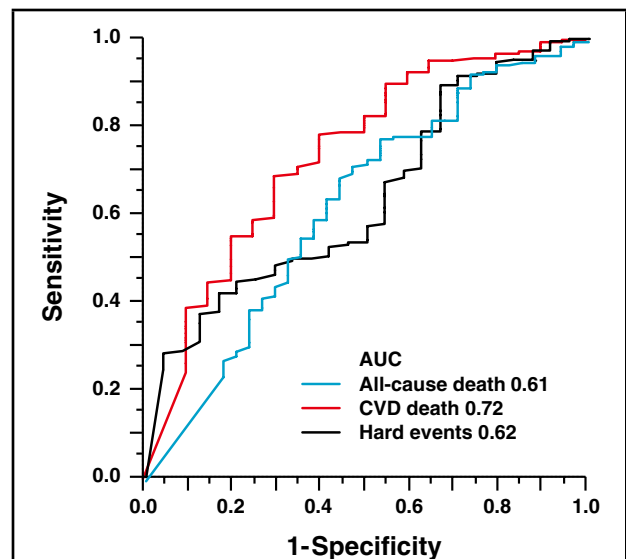

Figure 2. Predictive values for all-cause and cardiovascular mortalities, and hard events in receiver operating characteristic analysis. The red line indicates cardiac death, the blue line indicates all-cause death, and the black line indicates hard events. AUC, area under the curve.

lowest rates of freedom from all-cause death, cardiac death, and hard events with estimated 10 year-survival rates of 68%, 68%, and 67%, respectively (**Figure 3**).

A CAC score >1,000 had a 1.83-fold increased risk of death from all-cause compared with a CAC score 0–100 by univariate analysis (95%CI, 1.17–2.87; P=0.0088). However, after adjustment for age and sex, traditional coronary risk fac-
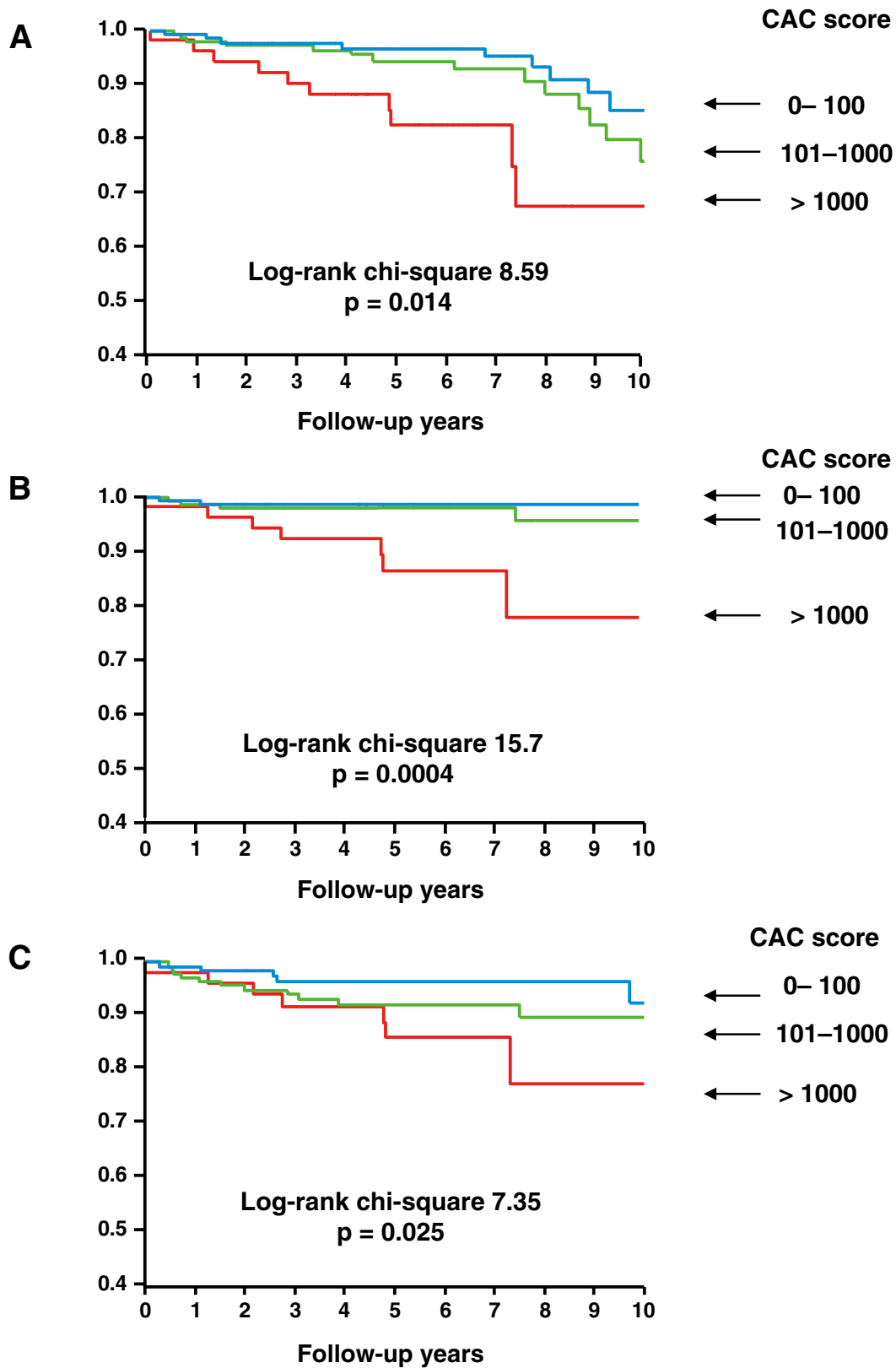
Figure 3. Unadjusted Kalpan–Meier event-free survival curves among 5 groups with stratified coronary artery calcium (CAC) scores. (**A**) Free from all-cause death. (**B**) Free from cardiac death. (**C**) Free from hard events (non-fatal myocardial infarction and cardiac death). The blue line indicates that the CAC score=0–100, the green line indicates 101–1,000, and the red line indicates >1,000.

Table 4. Unadjusted and Adjusted HR for Overall Outcomes Compared Among CAC Scores

	Unadjusted HR (95%CI)			Adjusted* HR (95%CI)		
	0–100	101–1,000	>1,000	0–100	101–1,000	>1,000
All-cause death	1	1.18 (0.79–1.80)	1.83 (1.17–2.87)	1	1.03 (0.58–1.87)	1.61 (0.85–3.15)
P value		0.41	0.0088		0.92	0.15
Cardiac death	1	1.37 (0.60–3.67)	3.22 (1.58–8.37)	1	1.30 (0.51–3.82)	2.98 (1.15–9.40)
P value		0.46	0.001		0.37	0.024
Hard events	1	1.44 (0.87–2.57)	2.11 (1.22–3.85)	1	1.56 (0.82–3.17)	2.14 (1.02–4.78)
P value		0.16	0.008		0.18	0.045

*Adjusted for age, sex, hypertension, hyperlipidemia, diabetes, cigarette smoking, previous MI, and requirement for revascularization.
Abbreviations see in Tables 1,3.

tors, previous MI, and the need for revascularization, the HR was not statistically significant (HR, 1.61; 95%CI, 0.85–3.15; P=0.15). Patients with a CAC score >1,000 had a 3.22-fold increased unadjusted risk of cardiac mortality (95%CI, 1.58–8.37; P=0.001) and the adjusted HR was still significant (HR, 2.98; 95%CI, 1.15–9.40; P=0.0024). In addition, a CAC score >1,000 had a 2.11-fold increased risk for hard events (95%CI, 1.22–3.85; P=0.008) and the adjusted HR remained significant (HR, 2.14; 95%CI, 1.02–4.78; P=0.045) (**Table 4**).

Discussion

In the present study, we evaluated Japanese CAD patients who underwent coronary angiography and were followed-up for 6.0±2.4 years. We demonstrated that both the prevalence of angiographic CAD and a need for revascularization therapy had a positive relationship with an increase in CAC scores. In addition, we found that a higher CAC score had predictive value for future coronary events. Patients with a CAC score >1,000 had 2.98- and 2.14-fold higher risks for cardiac death and hard events, respectively, compared with those who had a CAC score 0–100.

The present study supports the usefulness of the CAC score as a predictor for future events in Asians. For approximately 2 decades, there have been cumulative reports regarding the usefulness of CAC scores for the prevalence of CAD and future coronary events in both asymptomatic and symptomatic subjects in Western countries.[5–8] However, there are few data in the Asian population. The MESA demonstrated that CAC scores have predictive value for future coronary events regardless of 4 ethnic groups (Caucasian, African American, Hispanic, and Asian) living in the USA.[6] However, in this cohort study, only 11.9% were Asians, and the adjusted HR ratio (1.25; 95%CI, 0.95–1.63, P=0.11) for major coronary events was not significant among Asian participants, who only had 6 such events. Further studies that evaluate the association between CAC scores and long-term coronary events are required in Asian populations.

Our data are similar to previous reports[21–23] of CAC scores for angiographic CAD patients. Moehlenkamp et al demonstrated that symptomatic male patients with a CAC score >1,000 had a 2.5-fold relative risk compared with those with a zero CAC score, and they concluded that a CAC score >1,000 might be a useful additional threshold for clinical risk stratification in patients with extreme coronary atherosclerosis.[21] Keelan et al also studied clinically stable patients undergoing coronary angiography including 89% of cases with chest pain and demonstrated that event-free survival was 3.2-

fold higher for patients with a CAC score <100 than for those with a CAC score ≥100.[22]

Since recent reports have shown that CAC scores should be used for re-stratification in intermediate-risk patients,[7,8] further population-based studies are required in Japanese individuals. Recently, from a meta-analysis in 9,592 patients with a median follow-up of 20 months, coronary CTA has been in clinical use to predict future cardiovascular events and death.[23] Symptomatic patients with suspected CAD, considerably intermediate-risk patients, are often referred to have coronary CTA. Obstructive findings in CTA have prognostic values for predicting future cardiovascular events.[23] Meanwhile, it has not been fully elucidated whether evaluation for non-calcified plaques has the potential to detect future cardiac events or whether this predictive value is superior to that using the calcium score. Detection of coronary stenosis and evaluation of non-calcified plaques in high CAC score patients could be unreliable. Patients with a high CAC score (>600) were excluded to assess diagnostic performance of CTA in a CoRE-64 multicenter study.[9] Because of blooming artifacts, heavy calcification in the coronary artery changes the visualization of the vessel lumen and plaque characteristics, and patients with a high CAC score should avoid undergoing coronary CTA. These findings suggest that it is appropriate to evaluate the predictive value of CAC scores for long-term cardiovascular events in such high-risk patients.

Our study included approximately 43% of patients who had index revascularization after CAC screenings. A need for revascularization therapy was not found to be an independent predictor of cardiovascular events or survival. In patients with a CAC score >1,000, revascularization therapy was carried out in approximately 70% of angiographic CAD patients. This proportion is comparable with a previous study demonstrating that 70% of patients who had a CAC>1,000 underwent revascularization.[21] These finding suggest that patients with CAC score >1,000 would be recommended to undergo invasive coronary angiography without coronary CTA. However, this issue should be further investigated.

We found that patients with a zero CAC score had a favorable prognosis to exclude future cardiac death and non-fatal MI. However, in the follow-up period, we found 1 hard event of sudden cardiac death and 6 non-cardiac deaths (3 with cerebrovascular disease, 2 with renal failure, and 1 malignancy). Recent studies have also shown that the absence of CAC suggests no significant CAD or future cardiac events.[24–26] However, the absence of CAC does not appear to completely exclude obstructive CAD or the need for revascularization in patients with coronary angiography. A previous study found

that angiographic CAD with >50% stenosis was found to be 19% and revascularization was performed in 12% of absent CAC patients.[27] The present study only had 1 case of with coronary events. Our study included 5% of patients with significant CAD, which is lower than the report by Gottlieb et al,[27] but it is similar to other reports.[22–24] In our study, acute coronary syndrome was excluded and approximately 20% of asymptomatic patients underwent angiography because of electrocardiogram abnormalities or positive stress tests.

Study Limitations

In the present study, enrolled patients underwent cardiac CT for CAC scores between 1993 and 2005, and they were followed-up for a mean of 6.0 years (range, 1–10 years). In this period, 2 types of CT machines, electron beams, and multidetector CT technology, were used. The correlation of CAC scores between the 2 CT scanners was high (r^2=0.955) and the agreement in cardiovascular risk stratifications was excellent (Cohen κ value=0.929).[19] Therefore, the CT scanner bias was negligible. In addition, it has been reported that interscan variability between these 2 scanners is similar.[28]

We have few data to evaluate the predictive values of CAC scores in intermediate-risk Japanese patients. Unlike the CAC score is recommended for use as a re-classified factor in intermediate-risk group patients into high or low groups in Western countries,[7] CAC measurements were not considered to be important in our countries. However, in our study of patients undergoing invasive coronary angiography, we have demonstrated that the CAC score has a highly predictive value. Despite the increased recent use of multidetector-row CT coronary angiography, CAC scores are still useful for identifying high-risk patients as well as for evaluation of vulnerable non-calcified plaques.

Because the prevalence of a need for revascularization therapy had a positive relationship with an increase in CAC scores, we assumed that there was a high probability of intervention-related events. However, we could not evaluate this issue. The present study is the first report to investigate the association between CAC scores and long-term prognosis, even in a high-risk population, and it is expected to result in a fundamental database for CTA-based coronary assessment, not only in Japan, but also worldwide. Further prospective multicenter studies investigating CAC scores as a predictor for cardiac mortality in Japanese intermediate-risk patients are required and should be compared with previous data from Western countries.

Conclusion

The CAC score has a predictive value for angiographical CAD and long-term mortality from cardiac disease in Japanese high-risk patients who undergo invasive coronary angiography.

Disclosure

Conflict of interest: none.

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