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ORIGINAL ARTICLE
Ischemic Heart Disease

Incremental Benefit of Coronary Artery Calcium Score Above Traditional Risk Factors for All-Cause Mortality in Asymptomatic Korean Adults

Donghee Han, MD; Bríain ó Hartaigh, PhD; Heidi Gransar, BSc; Ji Hyun Yoon, MD; Kwang-Joon Kim, MD, PhD; Min-Kyoung Kim, MD; Su-Yeon Choi, MD, PhD; Jidong Sung, MD, PhD; Hyuk-Jae Chang, MD, PhD

Background: Coronary artery calcium score (CACS) is a well-recognized marker for subclinical coronary atherosclerosis, particularly in asymptomatic populations. To date, however, the added prognostic benefit of CACS compared with traditional risk factors in an Asian population remains unknown. This study therefore investigated the benefit of CACS over traditional risk factors for all-cause mortality in a large multicenter registry of asymptomatic Korean adults.

Methods and Results: A total of 34,386 individuals were retrospectively enrolled to participate in a general health examination. The Framingham 10-year risk score (FRS) was calculated according to the traditional risk stratification algorithm and CACS was calculated in log(CACS+1) for continuous data and categorized as 0, 1–100, 101–400 and >400. During a median follow-up of 4.9 years (IQR, 3.0–7.1), there were 303 all-cause deaths (0.9%). Following adjustment, CACS was independently associated with all-cause death (hazard ratio, 1.10; 95% confidence interval (CI): 1.05–1.17; P<0.001). Notably, CACS added further prognostic value above and beyond FRS (likelihood ratio, X^2=75.42, P<0.001; continuous net reclassification improvement=0.40, 95% CI: 0.29–0.51, P≤0.001; improving C-statistic from 0.64, 95% CI: 0.61–0.67 to 0.68, 95% CI: 0.64–0.71; ΔC=0.04, 95% CI: 0.01–0.06, P=0.002).

Conclusions: In an asymptomatic Korean population, CACS improved prediction of all-cause mortality over and above that of a conventional risk tool. (*Circ J* 2015; **79:** 2445–2451)

Key Words: Computed tomography; Coronary artery calcium; Framingham risk score; Risk assessment

The accurate prediction of cardiovascular risk in asymptomatic individuals is an important dimension of primary prevention medicine.[1] Risk prediction models, namely the Framingham 10-year risk score (FRS), have been widely used for the prediction of risk of future cardiovascular events.[2,3] Nevertheless, prior studies have shown that these models have low predictive power for the estimation of cardiovascular risk depending on different populations and patient groups.[4–8]

Coronary artery calcium score (CACS) is a well-known robust surrogate for predicting cardiovascular risk and has been reported to add further prognostic benefit over and above traditional risk prediction algorithms in prior studies.[9–13] Despite this, the prevalence and predictive value of CACS tends to vary according to ethnicity.[14–17] To date, the extant CACS literature has typically focused on populations from Western societies and, consequently, little is known about the value of CACS in addition to conventional risk factors in other (eg, Asian) populations.

We therefore investigated the prognostic utility of CACS and whether it adds further value above FRS in a large multicenter observational registry of asymptomatic Korean adults followed for all-cause death.

Methods

Subjects

We utilized data on patients enrolled in the KOrea Initiatives

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Division of Cardiology, Yonsei Cardiovascular Center, Yonsei University College of Medicine, Seoul (D.H., J.H.Y., H.-J.C.), Korea; Dalio Institute of Cardiovascular Imaging, New York-Presbyterian Hospital and the Weill Cornell Medical College, New York, NY (D.H., B.ó.H.); Department of Imaging, Cedars Sinai Medical Center, Los Angeles, CA (H.G.), USA; Severance Executive Healthcare Clinic, Severance Hospital, Seoul (J.H.Y., K.-J.K.); Division of Cardiology, Department of Internal Medicine, Healthcare System Gangnam Center, Seoul National University Hospital, Seoul (M.-K.K., S.-Y.C.); and Division of Cardiology, Department of Medicine, Sungkyunkwan University School of Medicine, Heart Stroke and Vascular Institute, Samsung Medical Center, Seoul (J.S.), Korea
Mailing address: Hyuk-Jae Chang, MD, PhD, Division of Cardiology, Yonsei Cardiovascular Center, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Korea. E-mail: hjchang@yuhs.ac

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Table 1. Baseline Subject Characteristics vs. CACS Category

	Total (n=34,386)	CACS category				P-value
		0 (n=22,182)	1–100 (n=8,810)	101–400 (n=2,400)	>400 (n=994)	
Age (years)	53.8±8.7	51.5±8.0	56.7±7.9	60.3±8.4	63.3±8.6	<0.001
Male	26,522 (77.1)	16,124 (72.7)	7,429 (84.3)	2,079 (86.6)	890 (89.5)	<0.001
BMI (kg/m^2)	24.4±2.8	24.2±2.8	24.8±2.8	25.0±2.8	24.8±2.8	<0.001
Current smoker	8,392 (24.4)	5,428 (24.5)	2,183 (24.8)	566 (23.6)	215 (21.6)	0.125
Past smoker	12,424 (36.1)	7,191 (32.4)	3,686 (41.8)	1,087 (45.3)	460 (46.3)	<0.001
Hypertension	9,646 (28.1)	4,548 (20.5)	3,294 (37.4)	1,186 (49.4)	618 (62.2)	<0.001
Diabetes mellitus	3,389 (9.9)	1,365 (6.2)	1,244 (14.1)	501 (20.9)	279 (28.1)	<0.001
Dyslipidemia	7,267 (21.2)	4,095 (18.5)	2,241 (25.5)	652 (27.3)	279 (28.3)	<0.001
TC (mg/dl)	197.3±34.4	197.4±33.8	198.3±35.0	195.6±37.4	188.0±35.7	<0.001
HDL-C (mg/dl)	52.8±13.3	53.5±13.6	51.5±12.7	51.2±12.6	50.7±12.8	<0.001
LDL-C (mg/dl)	125.5±30.9	125.7±30.5	126.9±31.3	122.7±32.7	116.3±31.4	<0.001
FRS	8.2±6.8	6.7±6.2	10.3±6.8	12.3±6.8	13.9±6.8	<0.001
Low (<10%)	21,328 (62.0)	15,890 (71.6)	4,270 (48.5)	905 (37.7)	263 (26.5)	<0.001
Low-intermediate (10–15%)	6,108 (17.8)	3,221 (14.5)	2,074 (23.5)	578 (24.1)	235 (23.6)	<0.001
High-intermediate (15–20%)	2,945 (8.6)	1,435 (6.5)	1,005 (11.4)	326 (13.6)	179 (18.0)	<0.001
High (>20%)	4,005 (11.7)	1,636 (7.4)	1,461 (16.6)	591 (24.6)	317 (31.9)	<0.001
All-cause mortality	303 (0.9)	129 (0.6)	95 (1.1)	43 (1.8)	36 (3.6)	<0.001

Data given as mean±SD or n (%). BMI, body mass index; CACS, coronary artery calcium score; FRS, Framingham 10-year risk score; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

on Coronary Artery calcification (KOICA) multicenter registry. The KOICA registry is a retrospective, single-ethnicity multicenter observational registry of self-referred subjects who underwent health examination at 3 healthcare centers across South Korea. A total of 48,903 participants were recruited between December 2002 and July 2014, and were followed for a median duration of 4.8 years (IQR, 2.7–6.7 years). Self-reported medical questionnaire was used to obtain information on smoking status, past medical history and family history of hypertension, diabetes mellitus, dyslipidemia, stroke, and ischemic heart disease. Clinical parameters included age, sex, body mass index, waist circumference, and lipid profiles. All data were acquired at the time of each visit to the health-care centers. Subjects with a prior history of stroke or ischemic heart disease (n=308, n=1,701), without an available CACS (n=569) or variables comprising FRS (n=11,939) were excluded. Hence, 34,386 subjects were included in the current analysis. For the purpose of assessing the long-term potential benefit of CACS when added to FRS, we additionally selected only those with a follow-up duration >5 years (n=16,879). The appropriate institutional review board committees approved the study protocol for all centers. Given that the study was designed retrospectively using medical records, informed consent was not obtained from participants. The primary endpoint was all-cause mortality. Ascertainment of mortality was determined by querying the Ministry of Security and Public Administration up until December 2014 for 2 centers, and September 2014 in the other remaining center.

CACS Measurement

CACS was measured using a >16-slice CT scanner. Specific CT scanner types used within each center included the Philips Brilliance 256 iCT, Philips Brilliance 40 channel multi-detector CT, Siemens 16-slice Sensation, and GE 64-slice Lightspeed. All 3 centers followed standard prospective or retrospective methods. CACS was subsequently calculated according to the methods described by Agatston et al.[18] CACS was calculated as log(CACS+1) for continuous data and categorized according to the following: 0, 1–100, 101–400, and >400.

Statistical Analysis

FRS was used for traditional risk stratification[3] and subjects were categorized as low (<10%), low-intermediate (10–15%), high-intermediate (15–20%), and high (>20%) risk.[19] Continuous normally distributed variables are reported as mean±SD and were compared using Student's t-test or Wilcoxon rank-sum test as appropriate for 2-group comparisons, or using 1-way ANOVA or Kruskal-Wallis test as appropriate for >2-group comparisons. Comparison of categorical variables was performed using the Pearson chi-squared test and categorical variables are reported as counts with proportions. Cumulative all-cause mortality event rates over time according to CACS categories were estimated using the Kaplan-Meier method and compared using log rank test. Annualized event rates were obtained by dividing number of deaths by person-years. Cox proportional hazards regression models were used to calculate the hazard ratios (HR) with 95% confidence intervals (CI) for all-cause mortality according to CACS categories, after verifying that the assumption of proportional hazards was met using Schoenfeld residuals, and further assessment of the models using Groennesby and Borgan goodness-of-fit tests. The added prognostic value of CACS over and above that of FRS was evaluated using the likelihood ratio (LR) chi-squared test, the difference (Δ) in C-statistic, and the continuous net reclassification improvement (cNRI). C-statistics estimates were compared using the DeLong et al method.[20] Two-tailed P<0.05 was considered statistically significant. Statistical analysis was performed using SAS (version 9. 3; SAS Institute, Cary, NC, USA) and STATA (version 14; StataCorp, College Station, TX, USA).

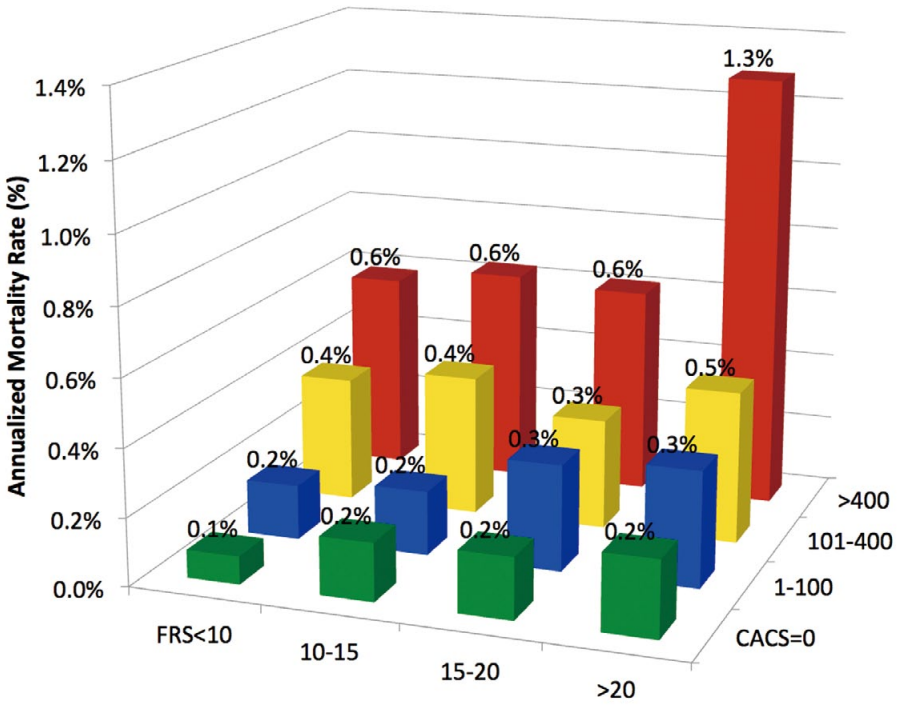

Figure 1. Annual event rate according to coronary artery calcium score (CACS) and Framingham 10-year risk score (FRS) in the whole group.

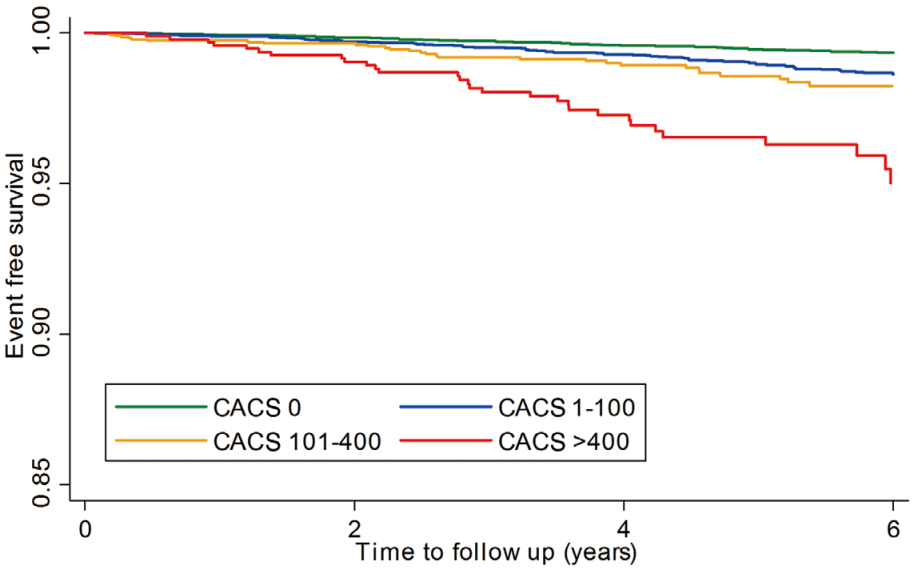

Figure 2. Kaplan-Meier curve for event-free survival according to coronary artery calcium score (CACS) category in the whole group.

Results

Baseline Characteristics

Clinical characteristics according to CACS categories are reported in Table 1. Mean subject age was 53.8±8.7 years. Participants were predominantly male (26,522; 77.1%), while hypertension, diabetes mellitus, and dyslipidemia were present in 9,646 (28.1%), 3,389 (9.9%), and 7,267 (21.2%) of the subjects, respectively. Older age and a higher proportion of men were more prominent with increasing CACS category. Likewise, the proportion of subjects with hypertension, diabetes, and dyslipidemia tended to increase with higher CACS category.

Table 2. Risk of Death From All Causes

	Univariate			Multivariate		
	HR	95% CI	P-value	HR	95% CI	P-value
Risk factor						
Age	1.10	1.09–1.12	<0.001	1.11	1.10–1.12	<0.001
Sex	1.58	1.15–2.19	0.005	1.52	1.03–2.25	0.036
Hypertension	1.53	1.21–1.94	<0.001	0.99	0.78–1.27	0.961
Diabetes mellitus	2.13	1.59–2.85	<0.001	1.39	1.03–1.88	0.032
TC per 10 mg/dl	0.96	0.93–1.00	0.030	1.00	0.97–1.04	0.861
HDL-C per 5 mg/dl	0.94	0.90–0.99	0.013	0.96	0.92–1.01	0.127
Smoking status						
Non-smoker	1.00			1.00		
Current smoker	1.30	0.97–1.76	0.082	1.74	1.23–2.47	0.002
Past smoker	1.40	1.07–1.83	0.014	1.23	0.90–1.68	0.199
FRS category†						
Low (<10%)	1.00			1.00		
Low-intermediate (10–15%)	1.88	1.40–2.53	<0.001	1.52	1.12–2.06	0.007
High-intermediate (15–20%)	2.30	1.61–3.29	<0.001	1.74	1.21–2.51	0.003
High (>20%)	3.29	2.46–4.40	<0.001	2.29	1.69–3.11	<0.001
CACS category						
0	1.00			1.00		
1–100	1.94	1.49–2.53	<0.001	1.13	0.86–1.50	0.374
101–400	3.75	2.65–5.30	<0.001	1.51	1.04–2.19	0.031
>400	7.89	5.44–11.43	<0.001	2.34	1.54–3.54	<0.001
CACS (continuous, log-transformed)	1.32	1.26–1.38	<0.001	1.10	1.05–1.17	<0.001

†Multivariate analysis of FRS category adjusted only by CACS category. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

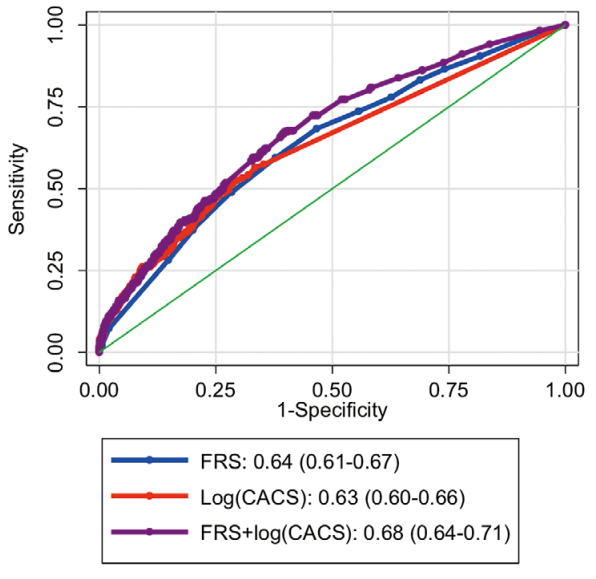

Figure 3. Receiver operating characteristic curves for prediction of all-cause mortality. CACS, coronary artery calcium score; FRS, Framingham 10-year risk score.

CACS Distribution and Clinical Outcome

In the low-FRS group (<10%), almost three-quarters of the study individuals had CACS zero (74.5%), while CACS >400 was present in only 1.2% (Table 1). Conversely, in the high-FRS group (>20%), less than half (40.9%) of patients had a zero CACS. Moreover, there was a parallel increase in FRS groups with higher CACS category. Over the course of the study period, a total of 303 individuals (0.9%) had experienced the primary endpoint. Foremost, low-risk individuals (FRS <10%) with CACS >400 had a total annualized event rate for all-cause death of 0.6% (95% CI: 0.3–1.2; Figure 1). Conversely, high-risk individuals (FRS >20%) with CACS=0 had an annual event rate of 0.2% (95% CI: 0.1–0.4), with rates being significantly different between CACS categories. In Figure 2, on Kaplan-Meier survival analysis, increasing CACS category was associated with increasing mortality.

CACS was independently associated with all-cause death (HR, 1.10; 95% CI: 1.05–1.17; P<0.001), and the crude risk of death for those with CACS>400 increased more than 2.3-fold compared with patients with CACS=0 (HR, 2.34; 95% CI: 1.54–3.54, P<0.001; Table 2). In subjects with CACS 1–100, however, there was no statistically significant difference in the risk of death from all-causes (HR 1.13 (0.86–1.50, P=0.374). After risk adjustment, each FRS category was statistically significantly associated with all-cause death.

Advantage of CACS Over FRS

Figure 3 shows receiver operating characteristic (ROC) curves for prediction of all-cause mortality. The mean area under the ROC curve (AUC) and 95% CI for FRS+log(CACS) were 0.68 (0.64–0.71), and that for FRS alone were 0.64 (0.61–0.67). The addition of CACS to FRS significantly improved prediction of all-cause mortality (LR χ^2=75.42, P<0.001; cNRI=0.40, 95% CI: 0.29–0.51, P≤0.001; and ΔC-statistic=0.04, 95% CI: 0.01–0.06, P=0.002; Table 3). In additional analyses, we assessed the long-term (ie, >5-year) improved

Table 3. Discrimination and Reclassification of CACS When Added to FRS

Characteristics	Total group (n=34,386)	Follow-up ≥5 years (n=16,879)
C-statistic for FRS (95% CI)	0.64 (0.61–0.67)	0.63 (0.59–0.67)
C-statistic for FRS+CACS (95% CI)	0.68 (0.64–0.71)	0.67 (0.64–0.71)
ΔC statistic (95% CI)	0.04 (0.01–0.06)	0.04 (0.02–0.07)
P-value	0.002	0.002
cNRI (95% CI)	0.40 (95% CI: 0.29–0.51)	0.42 (95% CI: 0.29–0.55)
P-value	<0.001	<0.001
% events (P-value)	–3% (0.605)	–7% (0.306)
% non-events (P-value)	43% (<0.001)	49% (<0.001)
Likelihood ratio χ^2	75.42	55.44
P-value	<0.001	<0.001

CACS, coronary artery calcium score (log-transformed); ΔC, difference in C-statistic; cNRI, category-free net reclassification index. Other abbreviations as in Tables 1,2.

benefit of CACS when added to the FRS. Among 16,879 subjects with long-term follow-up (median duration, 7.1 years; IQR, 5.9–8.4 years), adding CACS to FRS significantly improved the prediction of all-cause mortality (AUC for FRS+log(CACS)=0.67, 95% CI: 0.64–0.71; AUC for FRS alone=0.63, 95% CI: 0.59–0.67; LR χ^2=55.44, P<0.001; cNRI=0.42, 95% CI: 0.29–0.55, P<0.001; ΔC-statistic=0.04, 95% CI: 0.02–0.07, P=0.002).

Discussion

In this multicenter observational study, we evaluated the distribution of CACS and its added benefit over FRS in an asymptomatic Korean population, and found that CACS augments reclassification when added to the FRS. Further still, when added to FRS, CACS significantly improved prediction of all-cause mortality, especially in those with long-term (ie, beyond 5 years) follow-up duration.

FRS is a widely used tool for cardiovascular risk assessment, although previous studies suggest that this prediction tool may misclassify risk depending on which population it is being applied to.[4,21] Thus, in an effort to improve risk assessment in varying populations, it is recommended to explore alternative risk markers additional to FRS. To this end, CACS appears to be a useful adjunct to FRS when assessing cardiovascular risk, because CACS typically reflects atherosclerotic plaque burden in the coronary arteries.[22] Indeed, CACS has demonstrated prognostic value for cardiovascular events in an asymptomatic population setting, and its advantage in cardiovascular risk stratification is well recognized. For instance, Greenland et al reported that the addition of CACS to FRS produced significant improvement in the prediction of cardiovascular risk.[9] The Multi-Ethnic Study of Atherosclerosis (MESA) study also documented that CACS provided additional benefit over FRS, even among different ethnic groups.[23] In an additional study, Yeboah et al compared several novel risk markers for risk prediction in the MESA population.[10] The latter study indicated that these risk markers were all strong independent predictors of coronary artery disease (CAD), although CACS appeared to provide superior prediction as compared with the other novel risk markers.

In addition, CACS is considered to further improve risk stratification as advocated by recent guidelines.[24,25] The American College of Cardiology Foundation/Society of Cardiovascular Computed Tomography guidelines recommend that CACS is appropriate for CAD risk estimation in asymptomatic subjects presenting with intermediate risk.[24] The 2012 European Society guidelines for assessment of cardiovascular disease also recommend that computed tomography for coronary calcium should be used for cardiovascular risk assessment in asymptomatic adults at moderate risk.[26] In the most recent published guidelines to date, however, the 2014 American College of Cardiology/American Heart Association guidelines for the assessment of cardiovascular risk downgraded the recommendation level from IIa to IIb. We add, however, that this downgrade does not suggest that CACS cannot predict cardiovascular events. A pooled cohort of atherosclerotic cardiovascular disease patients has been used to define the new risk prediction tool in the present guidelines, which also includes cerebrovascular disease as a clinical outcome. Therefore, CACS may be an indicator of more than one of the manifestations of CAD.

A disparity in the prevalence and severity of CACS according to ethnicity has been noted. In MESA, Bild et al reported that CACS differed with ethnicity after adjusting for other risk factors.[14] Compared with Caucasian subjects, other ethnic groups had a lower relative risk for coronary calcification. Budoff et al found that after adjusting for age and several other risk factors, there was a lower prevalence and severity of coronary calcification in African-American and Asian subjects as compared with Caucasian subjects.[15] In a recent study, Fujiyoshi et al performed a cross-sectional comparison of CACS between Caucasian and Japanese men.[17] In that study, Caucasian men had a higher burden of coronary calcium than Japanese men. Moreover, this ethnic disparity varied according to age group, with the presence of coronary calcification becoming more prominent with advancing age. Taken together, these findings suggest that the CACS difference according to ethnicity may further be affected by other factors, primarily by well known traditional risk factors.

The present findings support, as well as extend, prior studies that investigated CACS compared with traditional risk factors in Korean populations. Kim et al evaluated the difference in risk stratification according to FRS and CACS in 7,988 Korean individuals considered to be at intermediate cardiovascular risk.[27] In that study, FRS appeared to underestimate cardiovascular risk in approximately 10% of the study population. This suggested that CACS should perhaps be considered useful for more accurate risk stratification, although that study was cross-sectional in nature and failed to describe clinical outcomes. Moreover, Park et al reported that the addition of CACS to FRS produced significant improvement in predicting

adverse cardiovascular outcome,[28] although it should be noted that the latter study focused primarily on the comparison of novel risk markers such as C-reactive protein or coronary stenosis on CT angiography, and therefore those results do not fully reflect discrimination and reclassification of CACS when added to FRS.

The present study has some limitations that should be noted. The present study was retrospective and observational in nature. Therefore, we cannot discount the potential for bias due to unmeasured confounding. All subjects in the KOICA registry were self-referred, which could have led to selection bias. The primary outcome in this study was all-cause mortality. Mortality events may not be entirely related to cardiovascular disease. Despite this, the use of all-cause death as the primary outcome in this study may lower the possibility of bias due to misreporting or misclassification of death, which can often be the case when utilizing cause-specific mortality as the primary endpoint.[29] Future studies should focus on the utility of CACS when added to FRS for cause-specific endpoints. Although the KOICA registry is large, this registry included asymptomatic individuals only, which clearly limits the number of events occurring during follow-up. FRS was traditionally validated in a Western population. Prior studies show that FRS tends to overestimate coronary risk in Asian populations.[21] Despite this limitation, this registry is the largest databank with regard to the use of CACS and the utility of its addition to FRS in an Asian population with a relatively long follow-up duration.

Conclusions

In this study involving a large sample of asymptomatic Korean adults, CACS successfully improved prediction of all-cause mortality when added to a number of traditional risk factors. In the light of these findings, CACS may be recommended for future risk stratification at least in an asymptomatic Korean population. Future studies to determine whether CACS improves risk prediction beyond FRS in other Asian cohorts are now warranted.

Acknowledgments

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Conflict of Interest

The authors report no relationships that could be construed as a conflict of interest.

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